Supplementary material

Exploring the backbone of enkephalins to adjust their pharmacological profile for the delta opioid receptor

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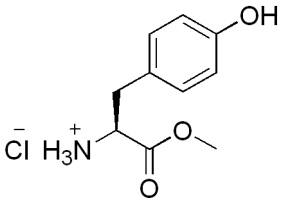
Experimental procedures and spectral data (same order as compounds appear in schemes 1-5)

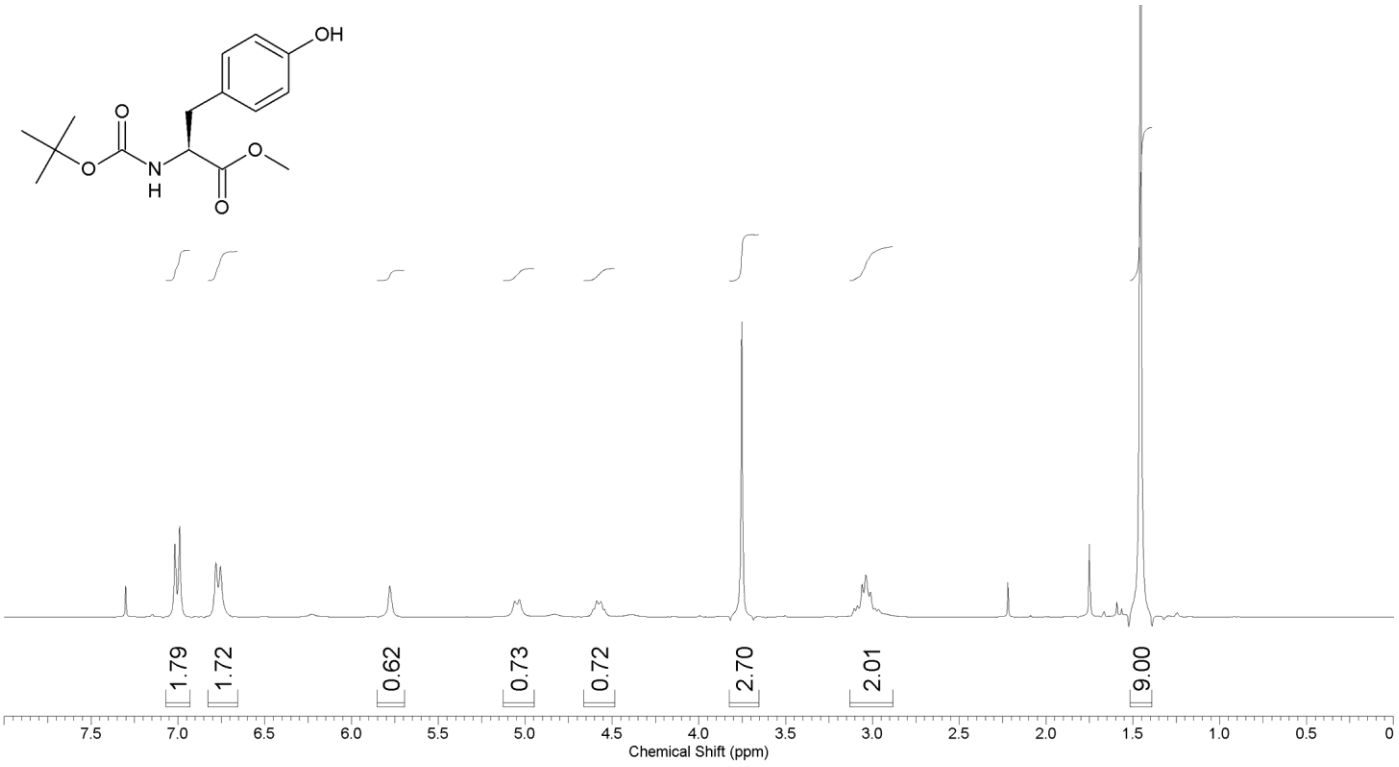
H-Tyr-OMe [1]



$SOCl_2$ was added (2.00ml, 27.5mmol) to a suspension of *l*-tyrosine (5.00g, 27.5mmol) in anh MeOH (50 ml) under an Ar atmosphere. The resulting solution was stirred for 16h at rt. The solvents were concentrated under vacuum. The crude solid obtained was washed with Et_2O to give the title product as a white solid (6.99g, 100%). **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.06 (d, 2H, *J*=8.5 Hz), 6.78 (d, 2H, *J*=8.5 Hz), 4.23 (t, 1H, *J*=7.1 Hz), 3.8 (s, 3H), 3.20-3.02 (m, 2H). **^{13}C NMR** (75 MHz, CD_3OD) δ (ppm) 169.1, 156.9, 130.2, 124.2, 115.5, 54.03, 52.2, 35.2. **IR** (KBr) ν (cm^{-1}) 3510-2680 (br), 1732, 1604, 1508. **MS (m/e, *rel intensity*)** 195 (MH^+, 12), 136 (40), 107 (100). **Exact mass :** calculated for $C_{10}H_{13}NO_3$: 202.2230, found: 202.03021. **$[\alpha]^{20}_D$** +12.0 (c=3.35, MeOH)

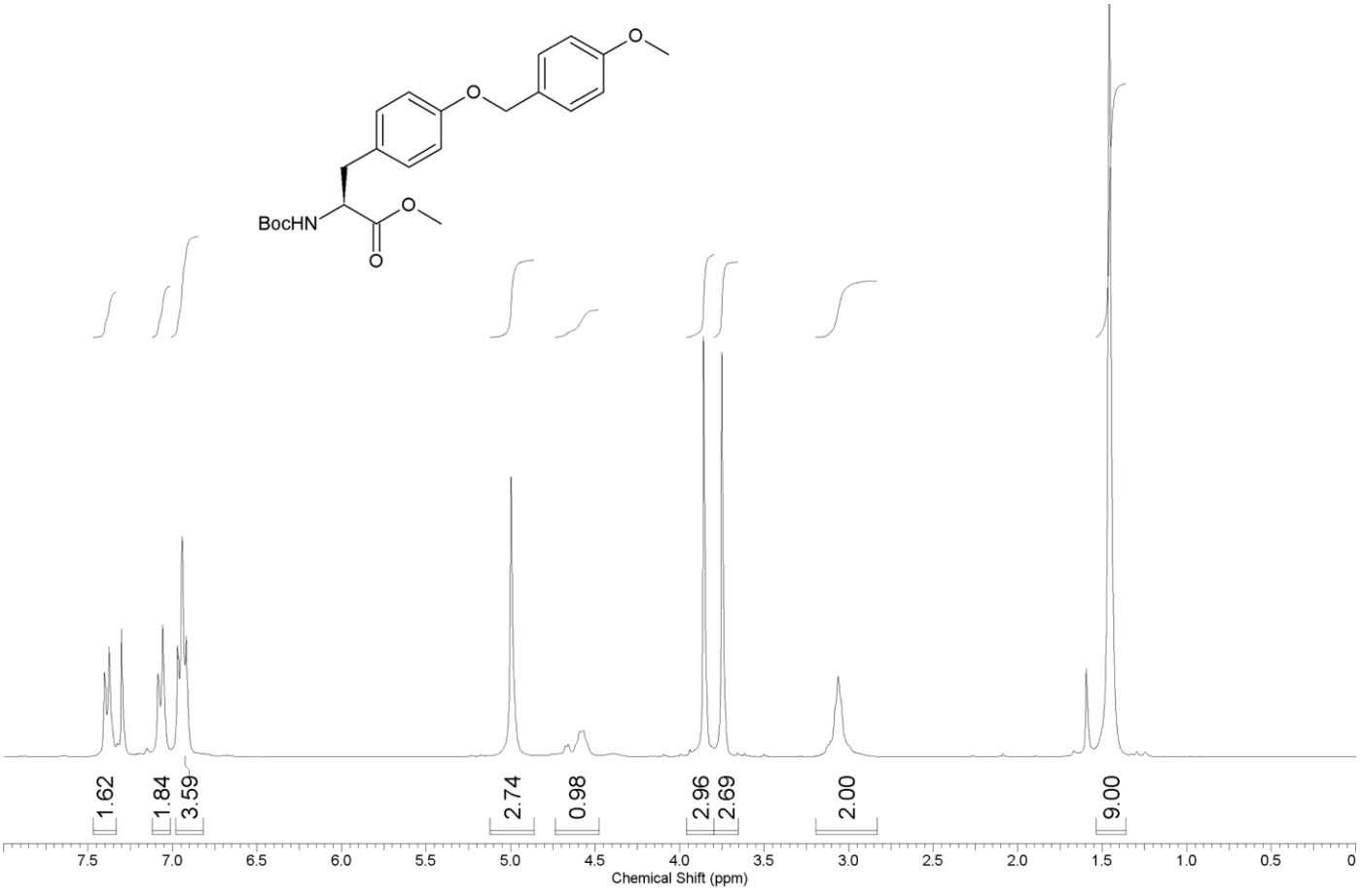
Boc-Tyr-OMe [1]

H-Tyr-OMe (3.10g, 13.4mmol) was dissolved in MeOH (50ml) and $NaHCO_3$ (2.36g, 28.1mmol) was added. The resulting mixture was stirred for 15min at rt. A solution of Boc_2O (3.20g, 14.7mmol) in MeOH (10ml) was then added and the reaction was stirred for 4h at rt. The mixture was dried under vacuum and dissolved in H_2O (400ml). The aqueous solution was acidified with 1N HCl until pH reached 4 then extracted with EtOAc (3 x 100ml). The combined organic phases were dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel using MeOH and DCM (1:19) to yield the title compound as a white solid (4.04g, 100%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 6.98 (d, 2H, *J*=8.4 Hz), 6.75 (d, 2H, *J*=8.4 Hz), 5.76 (s, 1H), 5.04 (br, 1H), 4.55 (br, 1H), 3.73 (s, 3H), 3.07-2.93 (m, 2H), 1.44 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm) 172.6, 155.3, 155.0, 130.4, 127.6, 115.5, 80.2, 54.6, 52.3, 37.6, 28.3. **IR** ($CHCl_3$) ν (cm^{-1}) 3615, 3018, 2399, 1711, 1513. **MS (m/e, *rel intensity*)** 295 (MH^+, 3), 178 (85), 107 (100). **Exact mass :** calculated for $C_{15}H_{21}NO_5$: 295.1420, found: 295.1426. **$[\alpha]^{20}_D$** +45.3 (c=2.94, $CHCl_3$)



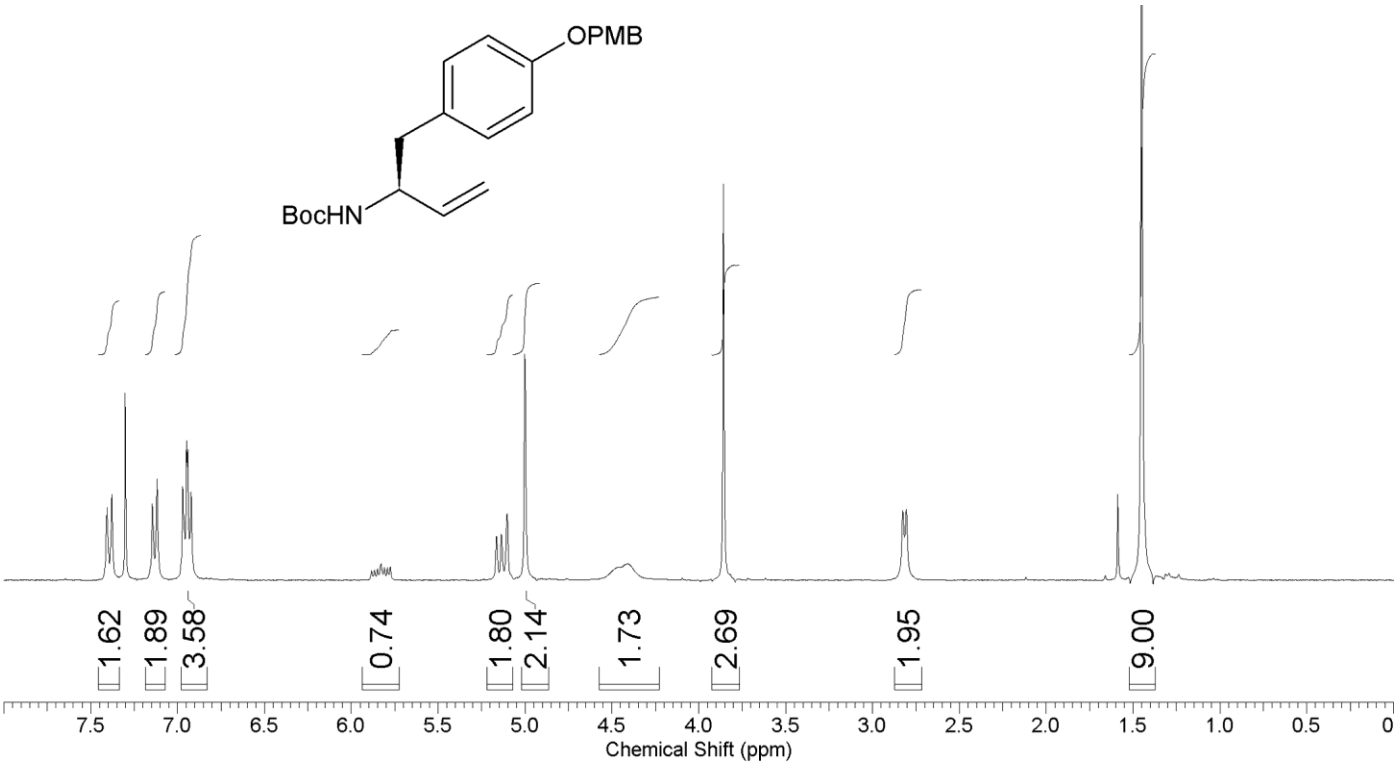
Boc-Tyr(PMB)-OMe (9) [2]

Boc-Tyr-OMe (3.74g, 12.7mmol), *p*-methoxybenzyl chloride (2.91ml, 20.9mmol), $Bu_4^+I^-$ (2.21g, 1.90 mmol) and Na_2CO_3 (2.90g, 20.9mmol) were dissolved in acetone (50ml). The reaction was refluxed for 40h. The resulting mixture was filtered, adsorbed on silica gel and purified by flash chromatography on silica gel using EtOAc and hexane (1:9). The title product was obtained as a white solid (4.48g, 85%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.36 (d, 2H, *J*=8.6 Hz), 7.03 (d, 2H, *J*=8.6 Hz), 6.93-6.88 (m, 4H), 4.96 (s, 3H), 4.55 (br, 1H), 3.82 (s, 3H), 3.70 (s, 3H), 3.07-2.98 (m, 2H), 1.42 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm) 172.4, 159.5, 158.0, 130.3, 129.2, 129.0, 128.1, 114.9, 114.0, 79.9, 69.8, 55.3, 54.5, 52.2, 37.5, 28.3. **IR** ($CHCl_3$) ν (cm^{-1}) 3434, 3018, 2399, 1711, 1513. **MS (m/e, *rel intensity*)** 415 (MH^+, 10), 256 (10), 121 (100). **Exact mass :** calculated for $C_{23}H_{29}NO_6$: 415.1995, found: 415.2001. **$[\alpha]^{20}_D$** +37.6 (c=2.70, $CHCl_3$)

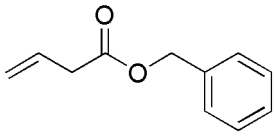


Alkene (11) [3]

The ether **9** (4.28g, 10.3mmol) was dissolved in anh DCM (50ml). The solution was cooled at -90°C, under an Ar atmosphere and DIBAL (15.7ml, 1.5M in toluene, 223mmol) was added dropwise during 15min. The reaction was stirred for an additional 15min and quenched slowly with MeOH. The mixture was adsorbed on silica gel and purified by flash chromatography on silica gel using EtOAc and hexane (3:7). The isolated aldehyde **10** was immediately dissolved in anh THF (30ml). Previously dried in toluene Ph_3PMeBr (4.78g, 13.4mmol) was dissolved in anh THF (100ml) under an Ar atmosphere and a solution of KHMDS (40.4ml, 0.28M in toluene, 11.3mmol) was added at 0°C. The solution was stirred for 15min and then cooled to -78°C. The solution of aldehyde was added slowly; the reaction was allowed to warm to rt and stirred for 16h. The resulting mixture was quenched with sat. NH_4Cl (300ml). The solvents were concentrated under vacuum and the aqueous phase was extracted with Et_2O (3 x 100ml). The organic phases were collected together, dried ($MgSO_4$) and adsorbed on silica gel. The crude mixture was purified by flash chromatography on silica gel eluting with EtOAc and hexane (from 1:4 to 2:3). The title compound was obtained as a white solid (2.32g, 59%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.37 (d, 2H, *J*=8.7 Hz), 7.11 (d, 2H, *J*=8.6 Hz), 6.95-6.90 (m, 4H), 5.88-5.75 (m, 1H), 5.17-5.08 (m, 2H), 4.98 (s, 2H), 4.45 (br, 2H), 3.83 (s, 3H), 2.79 (d, 2H, *J*=6.3 Hz), 1.43 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm) 159.4, 157.6, 155.2, 138.2, 130.5, 129.6, 129.2, 129.1, 114.7, 114.1, 114.0, 79.4, 69.8, 55.3, 53.6, 40.6, 28.4. **IR** ($CHCl_3$) ν (cm^{-1}) 3685, 3018, 2404, 1711, 1508. **MS (m/e, *rel intensity*)** 383 (MH^+, 2), 163 (37), 121 (100). **Exact mass :** calculated for $C_{23}H_{29}NO_4$: 383.2096, found: 383.2090. **$[\alpha]^{20}_D$** +11.9 (c=2.05, $CHCl_3$)



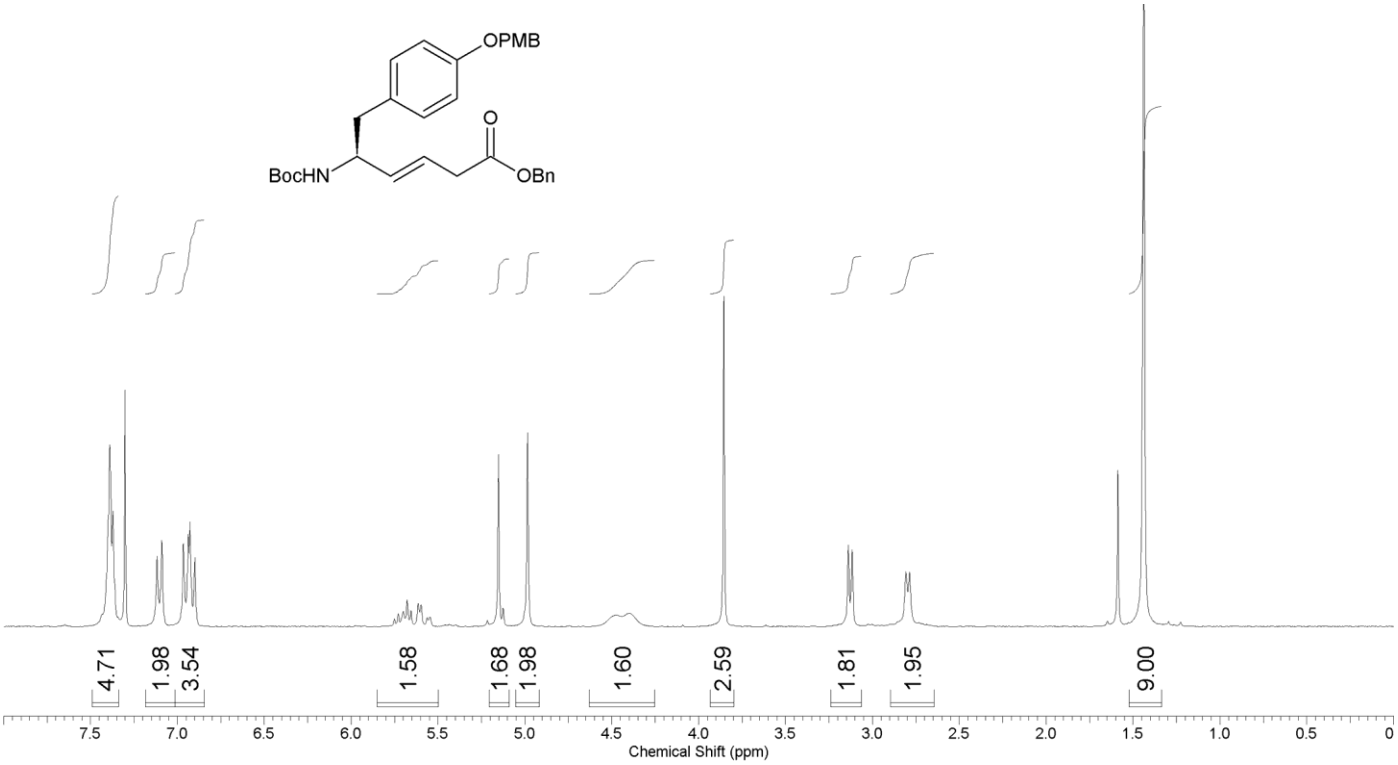
Alkene (12) [4]



A solution of benzyl chloroformate (7.02g, 41.1mmol) in anh DCM (30 ml) was added dropwise to a solution of vinyl acetic acid (3.22g, 37.4mmol) and pyridine (7.16g, 90.5mmol) in anh DCM (20ml). The resulting mixture was stirred for 16h at rt. The white precipitate was filtered off on Celite and the solution was washed with a saturated aqueous $CuSO_4$ (3 x 30ml), dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude oil was purified by flash chromatography on silica gel eluting with hex and Et_2O (from 1:0 to 19:1) to afford the title compound as a yellowish oil (4.77g, 72%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.45–7.3 (m, 5H), 5.95 (m, 1H), 5.25–5.15 (m, 4H), 3.15 (d, 2H, *J*=7.0 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm) 171.3, 135.9, 130.2, 128.6, 128.3, 118.7, 66.4, 39.1. **IR** (NaCl) ν (cm^{-1}) 3065, 3039, 2956, 1737, 1164. **MS (m/e, *rel intensity*)** 176 (M^+, 10), 91 (100). **Exact mass :** calculated for $C_{11}H_{12}O_2$: 176.0837, found: 176.0831.

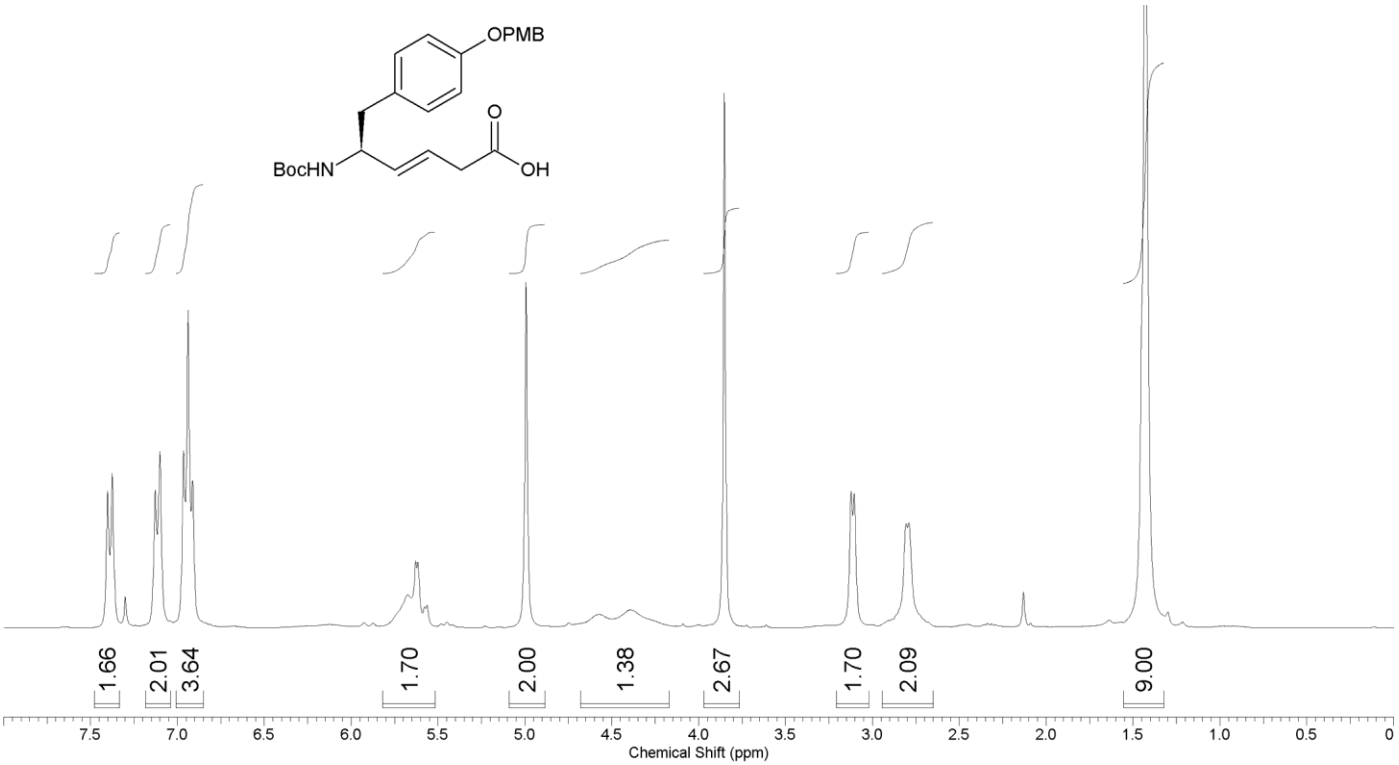
Tyr//Gly benzyl ester (13) [4]

The 2nd generation Grubbs catalyst (122mg, 0.145mmol) was added to anh DCM (10ml) under an Ar atmosphere. The suspension was purged with Ar for 5 min. A solution of alkene **11** (2.23g, 5.79mmol) and benzyl ester **12** (3.06g, 17.4mmol) in anh DCM (10ml) was added to the Grubbs catalyst. The solution was again purged with Ar for 5 min and refluxed for 40h. The mixture was adsorbed on silica gel and purified by flash chromatography on silica gel eluting with Et_2O and hexane (from 1:4 to 1:0). The title ester was obtained as a off-white solid (1.49g, 48%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.39-7.36 (m, 7H), 7.09 (d, 2H, *J*=8.4 Hz), 6.95-6.89 (m, 4H), 5.77-5.54 (m, 2H), 5.14 (s, 2H), 4.97 (s, 2H), 4.45 (br, 2H), 3.83 (s, 3H), 3.11 (d, 2H, *J*=6.4 Hz), 2.78 (d, 2H, *J*=6.5 Hz), 1.44 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm) 171.3, 159.4, 157.6, 155.1, 135.8, 134.2, 130.5, 129.5, 129.2, 129.1, 128.6, 128.3, 128.2, 122.3, 114.7, 114.0, 70.3, 69.8, 66.4, 55.3, 52.9, 40.7, 37.7, 28.4. **IR** ($CHCl_3$) ν (cm^{-1}) 3690, 3023, 2399, 1711, 1513. **MS (m/e, *rel intensity*)** 531 (MH^+, 1), 457 (50), 304 (100). **Exact mass :** calculated for $C_{32}H_{37}NO_6$: 531.2621, found: 531.2628. **$[\alpha]^{20}_D$** +3.09 (c=2.51, $CHCl_3$)

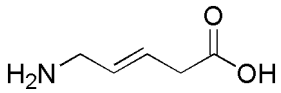


Tyr//Gly (14) [4]

The benzyl ester **13** (854mg, 1.60mmol) was dissolved in THF (10ml). LiOH (9.6ml, 0.5M in H_2O, 4.8mmol) was added and the reaction was stirred for 16h. The resulting mixture was dissolved in H_2O (10ml) and washed with EtOAc (3 x 20 ml). The aqueous phase was acidified with 1N HCl to reach pH 4 and extracted with EtOAc (3 x 15 ml). The organic extract were combined, dried ($MgSO_4$) and concentrated under vacuum. The crude compound was purified by flash chromatography on silica gel eluting with MeOH and DCM (from 1:99 to 1:9) to yield the title compound as a white solid (512mg, 72%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.37 (d, 2H, *J*=8.7 Hz), 7.09 (d, 2H, *J*=8.4 Hz), 6.95-6.89 (m, 4H), 5.68-5.55 (m, 2H), 4.98 (s, 2H), 4.45 (br, 2H), 3.84 (s, 3H), 3.11 (d, 2H, *J*=5.6 Hz), 2.78 (d, 2H, *J*=6.6 Hz), 1.42 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm) 176.4, 159.4, 157.6, 134.3, 132.9, 130.5, 129.2, 129.1, 122.0, 114.7, 114.0, 79.7, 69.8, 55.3, 52.9, 40.7, 37.3, 28.3. **IR** ($CHCl_3$) ν (cm^{-1}) 3615, 3023, 2399, 1515, 1214. **MS (m/e, *rel intensity*)** 441 (MH^+, 1), 214 (70), 121 (100). **Exact mass :** calculated for $C_{25}H_{31}NO_6$: 441.2151, found: 441.2154. **$[\alpha]^{20}_D$** +1.29 (c=0.37, $CHCl_3$)



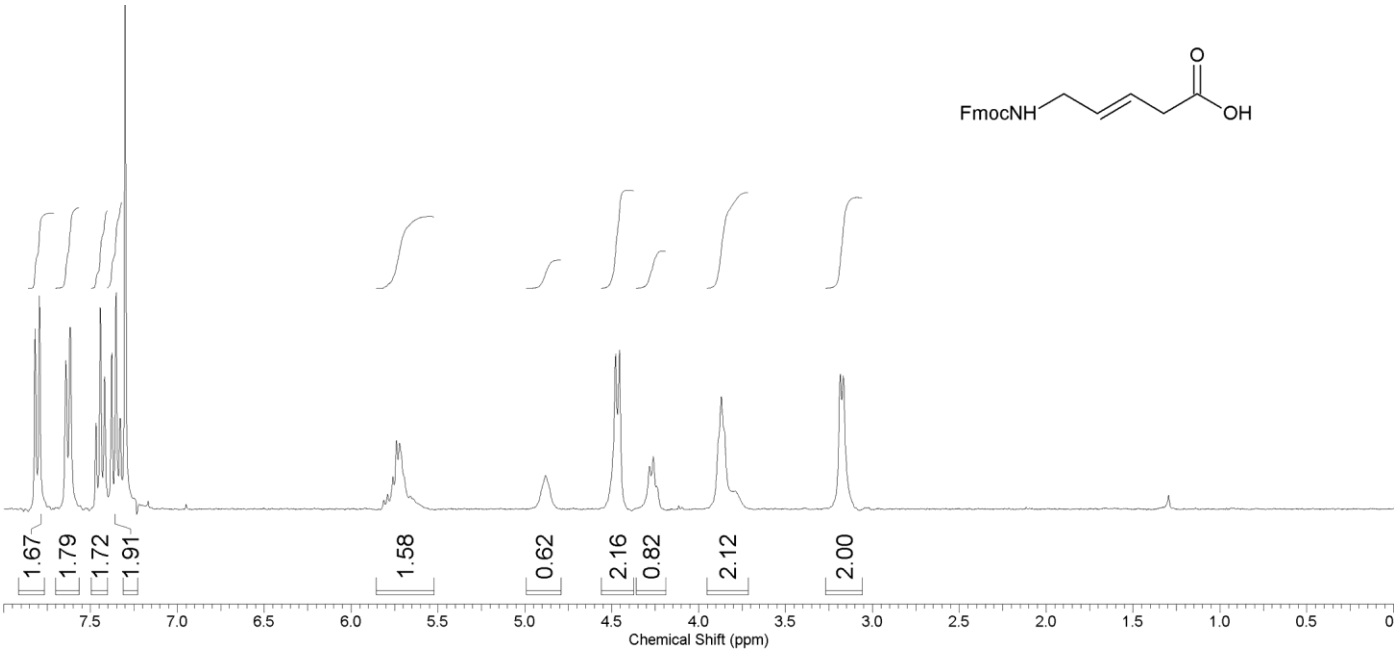
Gly//Gly (15) [5]



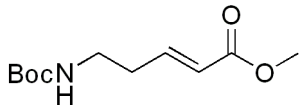
Commercially available trans-β-hydromuconic acid (30.0g, 207.9mmol) was dissolved in $CHCl_3$ (900ml) at 45°C under stirring. Conc H_2SO_4 (90ml) was then added, followed by small portions of NaN_3 (13.5g, 207.9mmol) over a period of 35 min. The viscous solution was stirred for 5h at 45°C and for 16h at rt. The resulting solution was extracted with H_2O (3 x 250ml) and the combined aqueous layers were diluted with H_2O (400ml) to dissolve small floating particles. Meanwhile, Dowex resin 50WX8-100 (650ml) was washed with de-ionized H_2O (1.5 l) and 0,1N HCl (1l). The resulting resin was then loaded with the aqueous extract, rinsed with deionized H_2O until pH 7. The product was finally eluted with 0,1N pyridine. All washings were performed under atmospheric pressure. The fractions with the desired title product were concentrated. The resulting white precipitate was filtered, rinsed with *i*PrOH and dried under vacuum (11.7g, 49%). **^{1}H NMR** (300 MHz, D_2O, TMS) δ (ppm) 5.86 (m, 1H), 5.50 (m, 1H), 3.45 (d, *J*=6.5 Hz, 2H), 2.87 ppm (d, 2H, *J*=7Hz); **^{13}C NMR** (75 MHz, D_2O, TMS) δ (ppm) 180.0, 132.8, 123.0, 40.8 ppm; **IR** (KBr) ν (cm^{-1}) 2800 br, 1630, 1560, 1490, 1370, 980. **MS (m/e, *rel intensity*)** 116 (MH^+). **Exact mass :** calculated for $C_5H_8NO_2$: 114.0555, found: 114.0553.

Gly//Gly fluorenylmethyl carbamate (16) [6]

The amino acid **15** (100mg, 0.860mmol) was dissolved in an aq solution of Na_2CO_3 10% (w/w) (2.3ml, 2.15mmol). Fmoc-Cl (222mg, 0.860mmol) was dissolved in THF (4ml) and slowly added to the aqueous solution under stirring at 0°C. The reaction was allowed to reach rt and stirred for 4h. The mixture was diluted in H_2O (100ml) and washed with Et_2O (2 x 15ml). The aqueous phase was acidified with 1N HCl to reach pH 4 and extracted with EtOAc (3 x 30ml). The organic phases were collected together, dried ($MgSO_4$) and concentrated under vacuum. The title product was obtained as a white solid (263mg, 90%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.76 (d, 2H, *J*=7.4 Hz), 7.59 (d, 2H, *J*=7.4 Hz), 7.43-7.38 (m, 2H), 7.34-7.28 (m, 2H), 5.70-5.62 (m, 2H), 4.83 (br, 2H), 4.42 (d, 2H, *J*=6.8 Hz), 4.24 (t, 1H, *J*=6.8 Hz), 3.89-3.75 (m, 2H), 3.14 (d, 2H, *J*=5.6 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm) 176.4, 143.9, 141.3, 130.8, 127.7, 127.1, 125.0, 123.6, 120.0, 66.7, 47.2, 42.5, 37.1. **IR** ($CHCl_3$) ν (cm^{-1}) 3599, 3018, 2394, 1524. **MS (m/e, *rel intensity*)** 337 (MH^+, 1), 178 (100), 165 (25). **Exact mass :** calculated for $C_{20}H_{19}NO_4$: 337.1314, found: .337.1312.



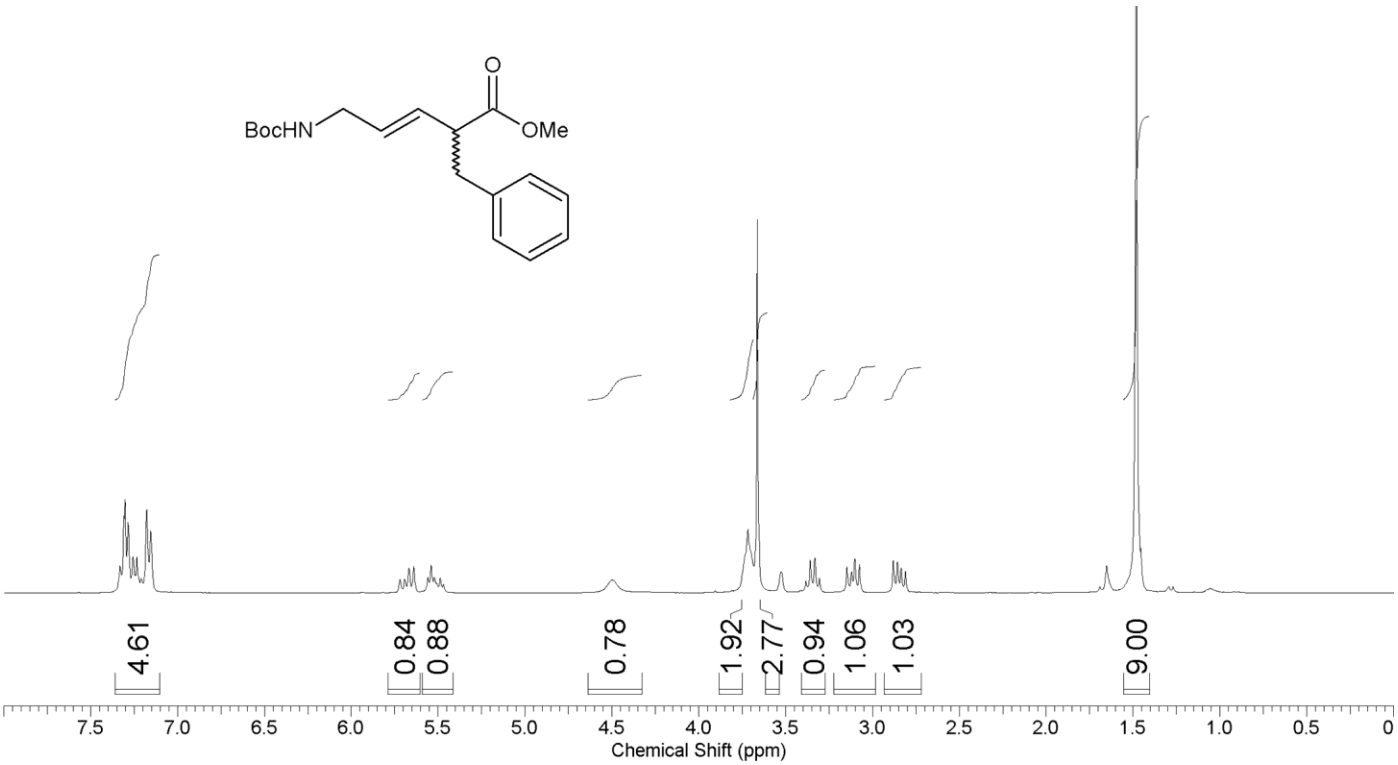
Conjugated δ amino acid methyl ester (18) [7,8]



3-amino-1-propanol **17** (6.09g, 80.9mmol), Boc_2O (18.5g, 84.9mmol) and $NaHCO_3$ (9.50g, 113mmol) were dissolved in DCM (60ml) and H_2O (200ml). The mixture was vigorously stirred for 16h at rt and the phases were separated. The aqueous layer was extracted with DCM (3 x 60ml). The organic extract were combined, aq 0.5N $NaHCO_3$ / 0.05N K_2CO_3 (270ml) was added and the mixture was vigorously stirred. Trichloroisocyanuric acid (7.50g, 32.4mmol) and TEMPO (60.0mg, 1.61mmol) were added and the mixture was stirred for 50min at rt. The two phases were separated and the aqueous phase was extracted with DCM (3 x 40ml). The organic phases were collected together, dried ($MgSO_4$) and methyl (triphenylphosphoranylidene) acetate (27g, 80,9g) was directly added to the solution at 0^oC. The reaction was allowed to warm to rt and stirred for 16h. The solution was concentrated under vacuum, dissolved in Et_2O and hexane. The solution was placed at 0^oC for 16h, filtered and concentrated under vacuum. The crude oil was purified by flash chromatography on silica gel eluting with EtOAc and hexane (from 3:17 to 3:7) to afford the title compound as colorless oil (7.51g, 40%). The spectroscopic data corresponded with those in the litterature.[8]

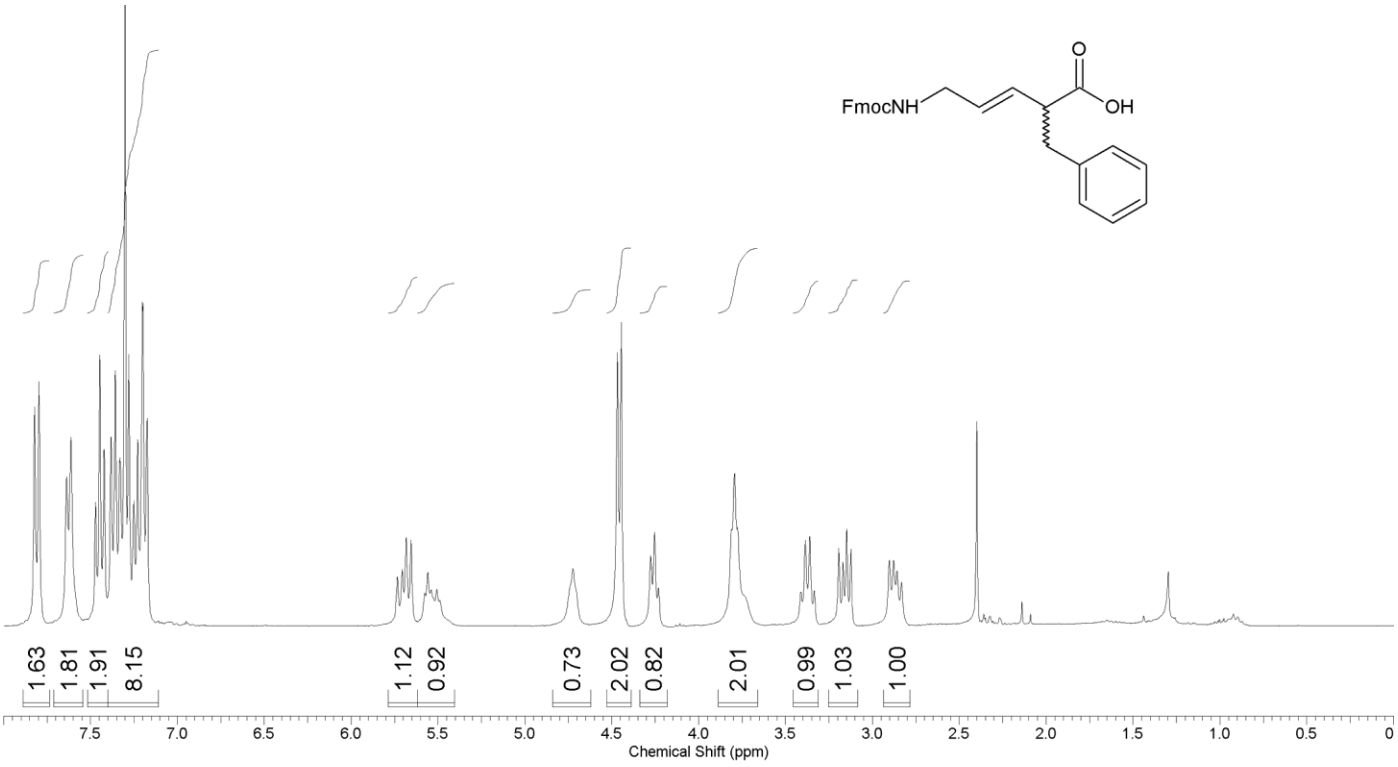
Gly//Phe methyl ester (19) [9]

n-Buli (6.6ml, 1.6M, 10.5mmol) was added to di-isopropylamine (1.44ml, 10.3mmol) under an Ar atmosphere at -10°C. The solution was stirred for 10 min, cooled to -78°C and anh THF (5ml) was added. A solution of the conjugated ester **18** (1.00g, 4.40mmol) in anh THF (10ml) was added slowly over 25min to the reaction. The mixture was stirred at -78°C for 30min and then benzyl bromide (0.73ml, 6.1mmol) was added. The reaction was again stirred for 4h, quenched afterward at -78°C with 15% (w/w) citric acid (10 ml) and H_2O (50 ml). The mixture was allowed to warm to rt. The THF was removed under vacuum and the aqueous phase was extracted with Et_2O (3 x 25ml). The combined organic phases were dried ($MgSO_4$) and adsorbed on silica gel. The crude product was purified by flash chromatography on silica gel using EtOAc and hexane (from 1:19 to 3:17). The title compound was obtained as a colorless oil (334mg, 24%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.29-7.11 (m, 5H), 5.63 (dd, 1H, *J*=8.5 and 15.5 Hz), 5.48 (dt, 1H, *J*=5.5 and 15.5 Hz), 4.45 (br, 1H), 3.70-3.63 (m, 2H), 3.29 (q, 1H, *J*=8.0 Hz), 3.06 (dd, 1H, *J*=8.0 and 13.5 Hz), 2.80 (dd, 1H, *J*=8.0 and 13.5 Hz), 1.43 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm) 173.8, 155.6, 138.5, 129.9, 129.0, 128.9, 128.3, 126.5, 79.4, 51.9, 50.6, 42.1, 38.7, 28.4. **IR** (KBr) ν (cm^{-1}) 3372, 2979, 1730, 1513. **MS (m/e, *rel intensity*)** 320 (MH^+, 20), 281 (100), 220 (43). **Exact mass :** calculated for $C_{18}H_{26}NO_4$: 320.1862, found: 320.1850.



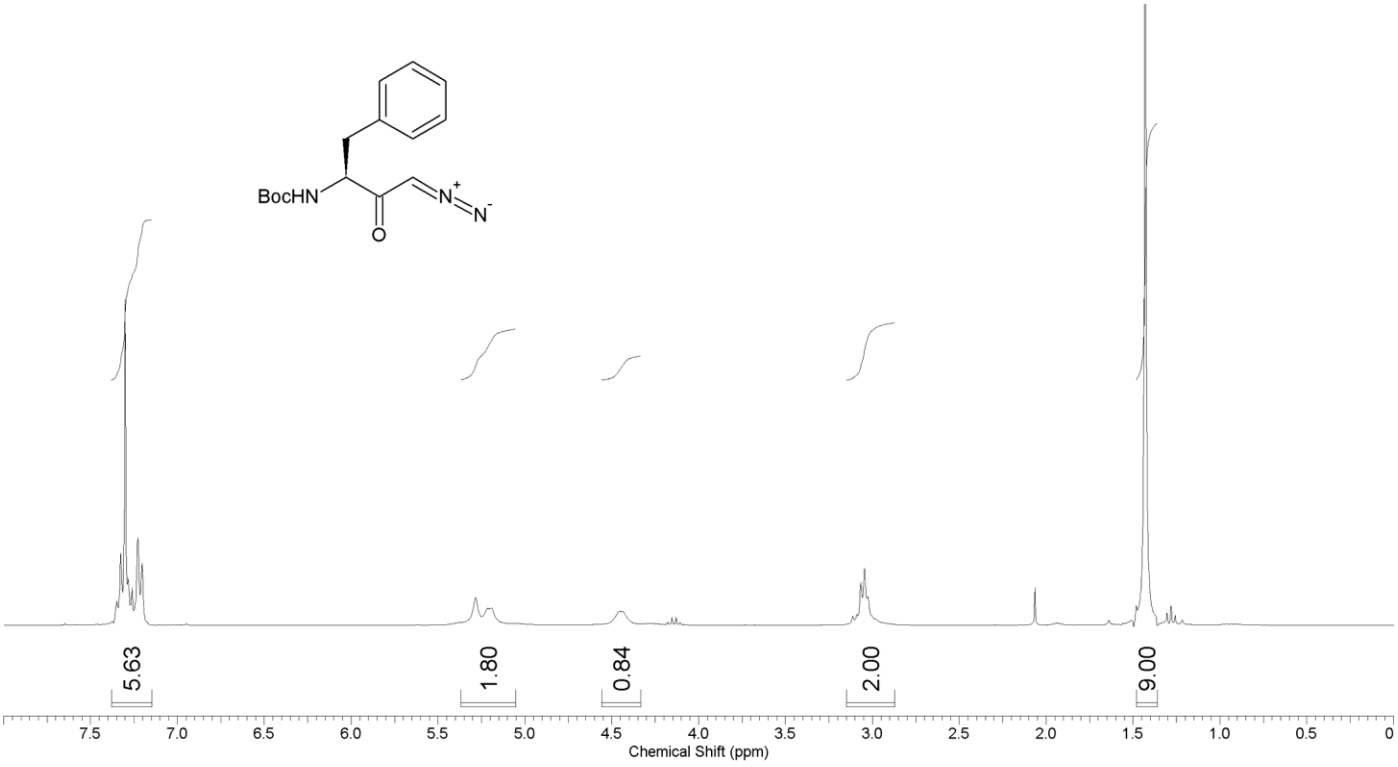
Gly//Phe fluorenylmethyl carbamate (20) [6]

The ester **19** (330mg, 1.03mmol) was dissolved in ACN (4ml) and 3N aq HCl (14ml). The solution was stirred for 16h at rt. The resulting mixture was concentrated under vacuum and dried using toluene three times. The crude salt obtained was dissolved in aq Na_2CO_3 (3.6ml, 1M, 3.6mmol). A solution of Fmoc-Cl (293mg, 1.13mmol) in THF (5ml) was added slowly to the aqueous mixture at 0°C. The reaction was allowed to warm at rt and stirred for 16 h. The resulting mixture was diluted in H_2O (100ml), acidified with 1N HCl to reach pH 2 and extracted using Et_2O (3 x 40ml). The organic extract were combined, dried ($MgSO_4$) and concentrated under vacuum. The crude compound was purified by flash chromatography on silica gel eluting with EtOAc, hexane and AcOH (30:69:1) to yield the title compound as a yellowish oil (389 mg, 88%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.76 (d, 2H, *J*=7.5 Hz), 7.58 (d, 2H, *J*=7.5 Hz), 7.40 (t, 2H, *J*=7.0 Hz), 7.34-7.13 (m, 7H), 5.65 (dd, 1H, *J*=8.5 and 15.5 Hz), 5.46 (dt, 1H, *J*=5.5 and 15.5 Hz), 4.68 (br, 1H), 4.41 (d, 2H, *J*=7.0 Hz), 4.21 (t, 1H, *J*=7.0 Hz), 3.75 (t, 2H, *J*=5.5 Hz), 3.33 (q, 1H, *J*=8.5 Hz), 3.06 (dd, 1H, *J*=8.0 and 13.5 Hz), 2.80 (dd, 1H, *J*=8.0 and 13.5 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm) 178.5, 156.3, 143.9, 141.4, 138.3, 130.0, 129.1, 129.0, 128.4, 128.4, 127.8, 127.1, 126.6, 120.0, 66.8, 50.4, 47.2, 42.5, 38.3. **IR** ($CHCl_3$) ν (cm^{-1}) 3408, 3068, 2948, 1712. **MS (m/e, *rel intensity*)** 428 (MH^+, 7), 206 (100), 178 (100). **Exact mass :** calculated for $C_{27}H_{26}NO_4$: 428.1862, found: 428.1848.



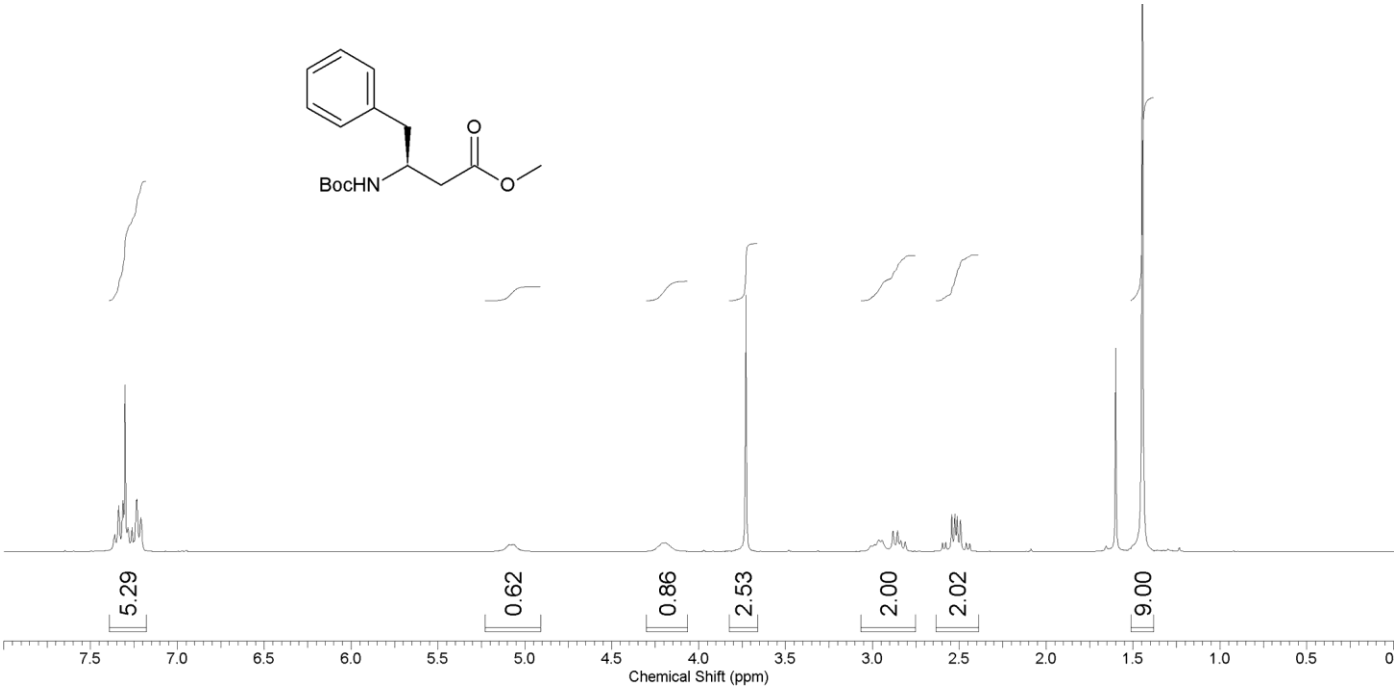
α-Diazoketone (21) [10]

Diazomethane was prepared by adding dropwise a solution of Diazald® in Et_2O to a stirring solution of KOH in EtOH and H_2O at 65°C. The solution of diazomethane in Et_2O was obtained by distillation of the mixture and used immediately. N-Boc-*l*-phenylalanine (11.3g, 42.3mmol) was dissolved in anh DCM (50ml). NMM (11.6ml, 105mmol) was added and the solution was stirred for 10min under an Ar atmosphere. The reaction was cooled down to -25°C and a solution of isobutylchloroformate (6.65ml, 50.9mmol) in anh DCM (25ml) was added slowly in 10min. The reaction was stirred at -25°C for 10 min. The salts formed were filtered and the resulting solution was again stirred at -25°C. The diazomethane (59.3mmol) solution was added. The reaction was allowed to warm to rt and stirred for 16h. The mixture was quenched using sat. NH_4Cl (20ml), H_2O (20ml) and 1N HCl (10ml). The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 25ml). The combined organic phases were dried ($MgSO_4$) and concentrated under vacuum. The crude compound was purified by flash chromatography on silica gel eluting with EtOAc and hexane (1:4) to yield the title compound as a yellow solid (9.93g, 81%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.35-7.19 (5H, m), 5.28 (1H, br), 5.19 (1H, br), 4.45 (1H, br), 3.12-2.98 (2H, m), 1.43 (9H, s). The spectroscopic data corresponded with those in the literature.[10]



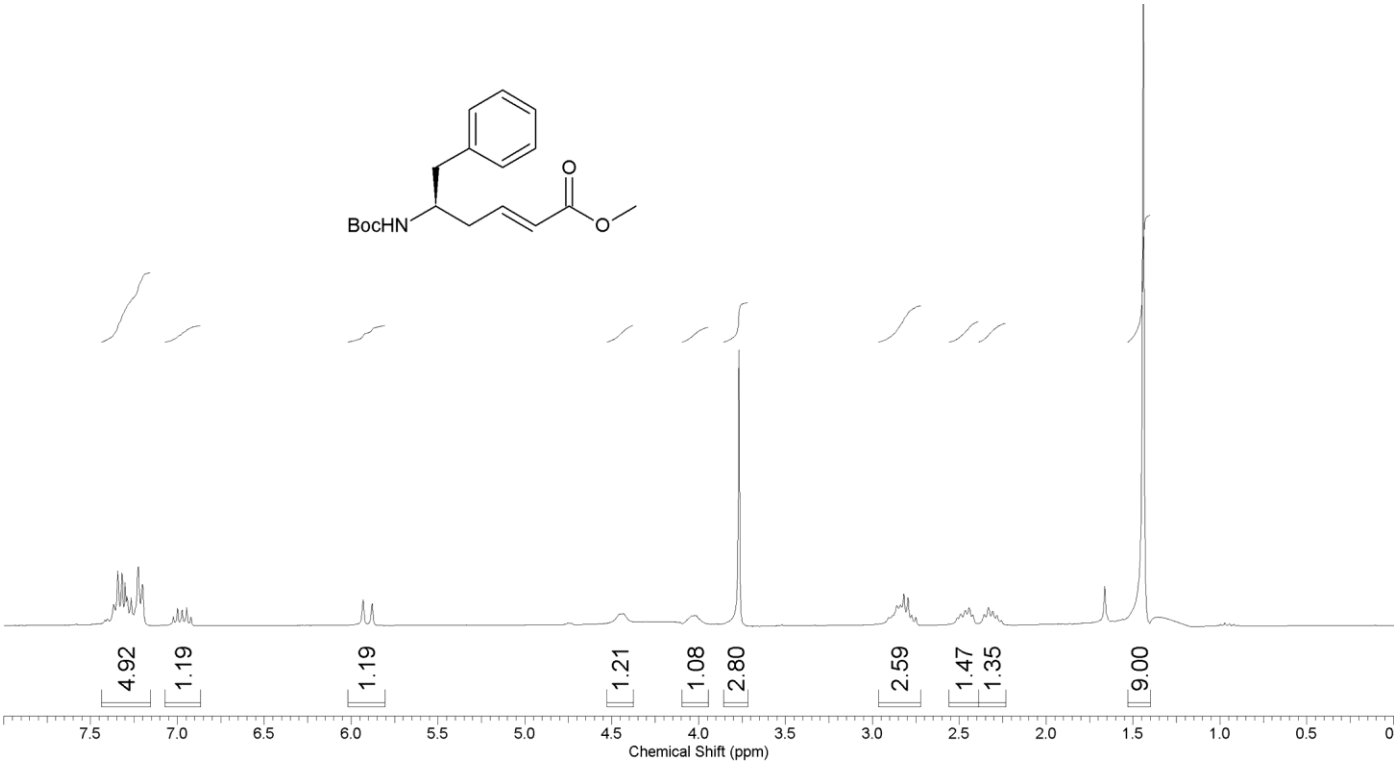
Methyl ester (22) [10]

The α-diazoketone **21** (9.93g, 34.3mmol) was dissolved in MeOH (100ml). A solution of silver benzoate (782mg, 3.43mmol) in NMM (5ml) was added dropwise at 0°C. The color of the reaction mixture became dark. It was stirred for 16h at rt. The resulting mixture was filtered through Celite and was concentrated to half the original volume under vacuum. The remaining solution was diluted in EtOAc (300ml) and washed with 1N HCl (3 x 100ml). The organic phase was dried ($MgSO_4$) and concentrated under vacuum. The mixture was purified by flash chromatography on silica gel eluting with EtOAc and hexane (from 3:17). The title ester was obtained as a white solid (9.30g, 93%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.36-7.19 (5H, m), 5.07 (1H, br), 4.20 (1H, br), 3.73 (3H, s), 3.03-2.80 (2H, m), 2.61-2.44 (2H, m), 1.43 (9H, s). The spectroscopic data corresponded with those in the literature.[10]



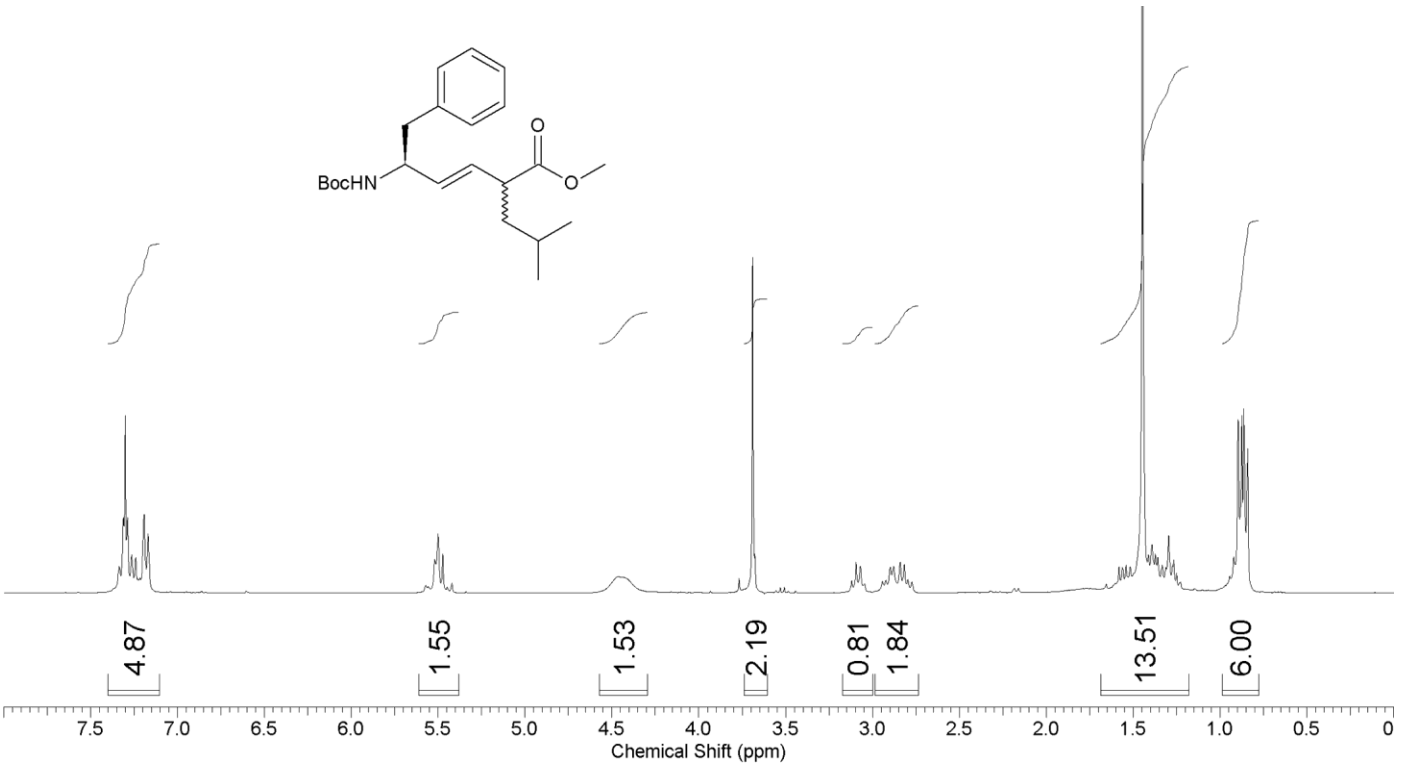
Conjugated δ amino acid methyl ester 24 [11]

The methyl ester **22** (9.30g, 31.7mmol) was dissolved in anh DCM (500ml) under an Ar atmosphere. The solution was stirred at -90°C and DIBAL (49ml, 1.5M in toluene, 73mmol) was added dropwise over 25min so that the temperature remained under -85°C. The reaction was stirred for 1h, then quenched slowly afterwards with MeOH (30ml). The mixture was adsorbed on silica gel and purified by flash chromatography on silica gel using EtOAc and hexane (1:4). The isolated aldehyde **23** (4.20g, 50%) was immediately dissolved in DCM (150ml) and methyl (triphenylphosphoranylidene) acetate (27g, 80,9g) was added to the solution at 0°C. The reaction was allowed to warm to rt and stirred for 16h. The solution was concentrated under vacuum, dissolved in Et_2O and hexane. The solution was placed at 0°C for 16h, filtered and concentrated under vacuum. The crude oil was purified by flash chromatography on silica gel eluting with EtOAc and hexane (3:17) to afford the title compound as white solid (4.50g, 87%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.43-7.17 (5H, m), 6.97 (1H, dt, *J*=16.0, 7.5 Hz), 5.91 (1H, d, *J*=16.0), 4.44 (1H, br), 4.01 (1H, br), 3.77 (3H, s), 2.92-2.73 (2H, m), 2.52-2.25 (2H, m), 1.44 (9H, s). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm) 166.6, 155.1, 144.9, 137.5, 129.4, 128.5, 126.6, 123.7, 79.5, 51.5, 50.7, 40.6, 36.5, 28.3. **IR** (NaCl) ν (cm^{-1}) 3436, 3366, 2978, 1713, 1659, 1497, 1366, 1169. **MS (m/e, *rel intensity*)** 320 (MH^+, 1), 228 (73), 129 (100). **Exact mass :** calculated for $C_{18}H_{26}NO_4$: 320.1862, found: 320.1866. **$[\alpha]^{20}_D$** -12.1 (c=0.96, $CHCl_3$)



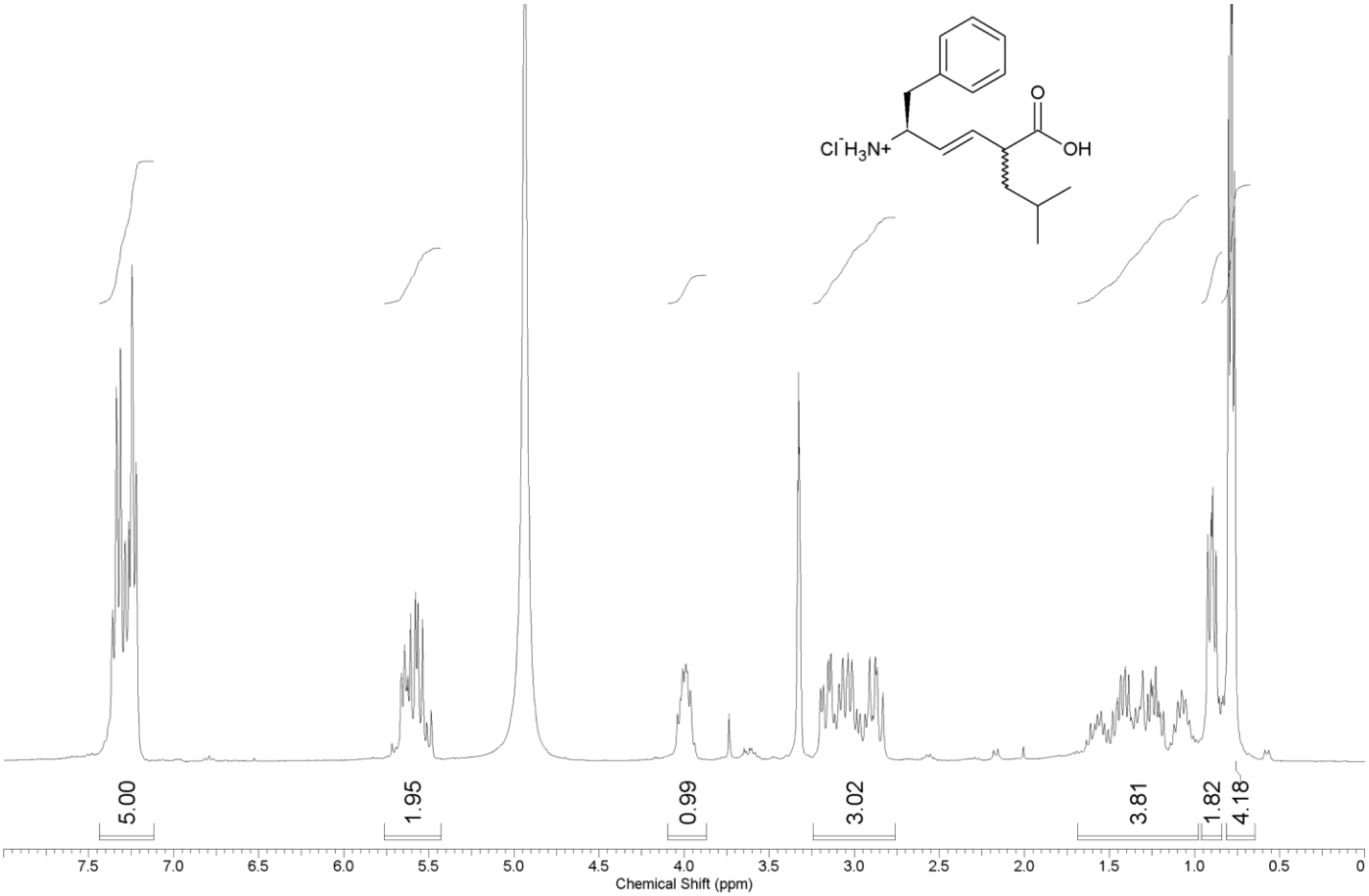
Phe//Leu methyl ester (25) [9]

n-Buli (12.2ml, 2.3M, 28.2 mmol) was added to di-isopropylamine (4.20ml, 30.1 mmol) and TMEDA (7.10ml, 47.0mmol) under an Ar atmosphere at -10°C. The solution was stirred for 10 min, cooled to -78°C and anh THF (50ml) was added. A solution of the methyl ester **24** (3.00g, 9.40mmol) in anh THF (50ml) was added slowly during 20min to the reaction. The mixture was stirred at -78°C for 15min and then isopropyl iodide (11.0 ml, 94.0 mmol) was added. The reaction was again stirred for 3h, quenched afterward at -78°C with brine (40ml). The solution was allowed to warm to rt and 1N HCl was added to reach pH 2. The THF was concentrated under vacuum and H_2O (200 ml) was added. The aqueous phase was extracted with Et_2O (3 x 100ml). The combined organic phases were dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel using EtOAc and hexane (from 1:9 to 3:17). The title compound was obtained as a colorless oil (569mg, 16%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.29-7.12 (m, 5H), 5.51 (dd, 1H, *J*=5.0 and 15.5 Hz), 5.41 (dt, 1H, *J*=7.5 and 15.5 Hz), 4.37 (br, 2H), 3.64 (s, 3H), 3.04 (q, 1H, *J*=7.5 Hz), 2.87 (dd, 1H, *J*=6.0 and 13.5 Hz), 2.76 (dd, 1H, *J*=7.0 and 13.5 Hz), 1.54-1.20 (m, 4H), 1.40 (s, 9H), 0.82 (dd, 6H, *J*=6.5 and 10.0 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm) 174.7, 155.0, 137.3, 132.3, 129.6, 128.8, 128.3, 126.4, 51.7, 46.9, 41.7, 41.2, 29.7, 28.3, 25.3,22.7,21.9. **IR** (NaCl) ν (cm^{-1}) 3373, 2954, 1709, 1500. **MS (m/e, *rel intensity*)** 376 (MH^+, 31), 259 (67), 184 (100). **Exact mass :** calculated for $C_{22}H_{34}NO_4$: 376.2488, found: 376.2478.



Phe//Leu (26) [9]

The methyl ester **25** (569mg, 1.03mmol) was dissolved in THF (20ml) and 6N HCl (60 ml). The solution was stirred at rt for 36h. The resulting mixture was concentrated under vacuum. The crude mixture was dissolved using H_2O and ACN. This solution was frozen and lyophilized. The title product was obtain as a yellowish powder (289mg, 72%). **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.36-7.17 (m, 5H), 5.67-5.44 (m, 2H), 3.99-3.89 (m, 1H), 3.15-2.82 (m, 3H), 1.59-1.00 (m, 3H), 0.86 (dd, 2H, *J*=6.5 and 9.0 Hz), 0.73 (dd, 4H, *J*=4.5 and 6.5 Hz). **^{13}C NMR** (75 MHz, CD_3OD) δ (ppm) 175.8, 135.9, 135.4, 129.3, 129.2, 128.4, 127.1, 126.8, 54.6, 40.7, 39.0, 24.7, 21.8, 20.6. **IR** (NaCl) ν (cm^{-1}) 3026, 2952, 1724, 1498. **MS (m/e, *rel intensity*)** 262 (MH^+, 100), 170 (52), 120 (15). **Exact mass :** calculated for $C_{16}H_{24}NO_2$: 262.1807, found: 262.1813.



Chlorotrityl resin peptide synthesis: [12]

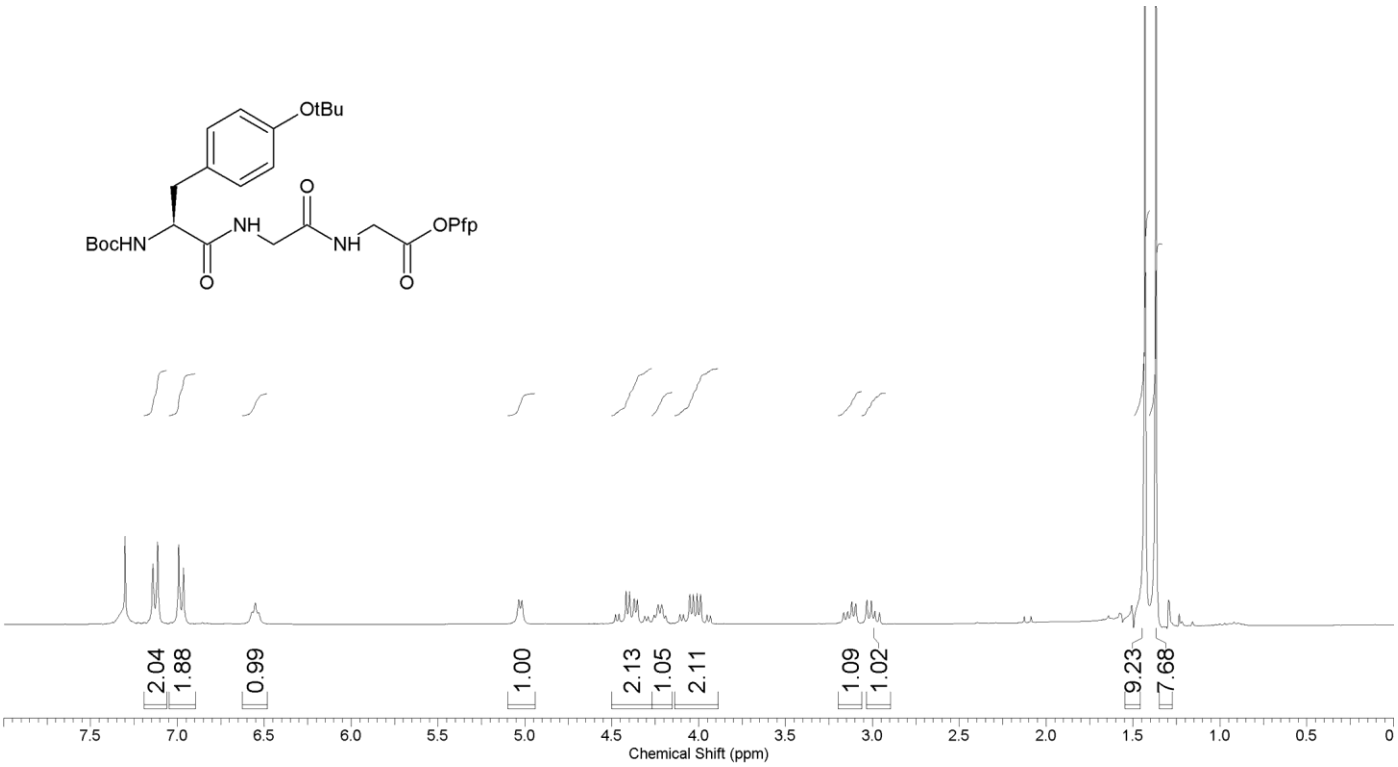
The resins are always washed using DMF (3x), *i*PrOH (3 x) and DCM (3 x), otherwise the solvents are mentioned explicitly. For cleavage of Fmoc, the resin was treated with 25% piperidine in DMF and the suspension was agitated in a shaker for 20 min. All couplings were performed using equals equivalents of protected amino acids and HBTU; with twice as many equivalents of NMM in DMF and the suspension was agitated in a shaker.

The protected peptide was synthesized manually using 2.5g of 2-Chlorotrityl chloride resin (loading: 1.3mmol/g). The initial coupling was achieved with Fmoc-glycine (1.10g, 3.57mmol), DIPEA (2.7ml), DMF (5ml) and DCM (2.5ml). The mixture was agitated in a shaker for 16h. The resin was washed with a solution of DCM/MeOH/DIPEA (17/2/1) 3 times, then DCM (3 x), DMF (3 x) and DCM (3 x). After drying under vacuum, loading was measured by UV quantification of Fmoc release. Final loading was found to be 0.59mmol/g.

The resin was deprotected and then washed. A coupling solution of Fmoc-Glycine (1.76g, 5.90mmol) and other previously mentioned couplings agents was added to the vessel and the suspension was agitated for 16h. The resin was washed, deprotected and then washed again. A coupling solution of commercially available Boc-Tyrosine(OtBu) (2.25g, 6.67mmol) was added to the vessel and the suspension was agitated for 16h. The resin was washed. The protected peptide was cleaved from the resin by 2 min treatment with 1% TFA in DCM (10 x 10ml) followed by washing with DCM (6 x 10ml) and MeOH (6 x 10ml). All washes and acid solutions were collected in test tubes containing (3ml) 10% pyridine in MeOH. The acid solution and subsequent washes were combined and concentrated up to 5ml under vacuum. H_2O (80ml) was added to the solution and 1N HCl was added to reach pH 3. The aqueous solution was extracted with EtOAc (3 x 25ml). The combined organic phases were dried ($MgSO_4$) and concentrated down to 5 ml under vacuum.

Boc-Tyr(OtBu)-Gly-Gly-OPFP (28)

Pentafluorophenol (375mg, 2.07mmol) and HOBt (51mg, 0.375mmol) were added to the crude solution of protected peptide **27**. DIC (0.530ml, 3.42mmol) was added dropwise and the mixture was stirred for 16h at rt. The resulting organic phase was washed with saturated aq $NaHCO_3$ (30ml) and H_2O (2 x 30ml). The combined organic phases were dried ($MgSO_4$) and adsorbed on silica gel. The mixture was purified by flash chromatography on silica gel using EtOAc and hexane (3:2). The title compound was obtained as a white solid (38.2mg, 4%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.08 (d, 2H, *J*=8.5 Hz), 6.94 (d, 2H, *J*=8.5 Hz), 6.50 (t, 1H, *J*=6.0 Hz), 4.98 (d, 1H, *J*=6.0 Hz), 4.39 (dd, 2H, *J*=6.0 and 18.0 Hz), 4.29 (dd, 2H, *J*=6.0 and 18.0 Hz), 4.18 (q, 1H, *J*=7.0 Hz), 4.02 (dd, 2H, *J*=6.0 and 17.0 Hz), 3.93 (dd, 2H, *J*=6.5 and 17.0 Hz), 3.09 (dd, 1H, *J*=7.0 and 14.0 Hz), 2.95 (dd, 1H, *J*=8.0 and 14.0 Hz), 1.39 (s, 3H), 1.33 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm) 172.3, 169.6, 165.9, 156.2, 154.5, 142.6, 139.4, 139.3, 136.2, 130.9, 129.6, 124.5, 81.0, 78.7, 56.8, 42.8, 40.4, 37.0, 28.8, 28.2. **IR** (NaCl) ν (cm^{-1}) 3311, 2980, 1801, 1664, 1518. **MS (m/e, *rel intensity*)** 617 (M^+, 100).

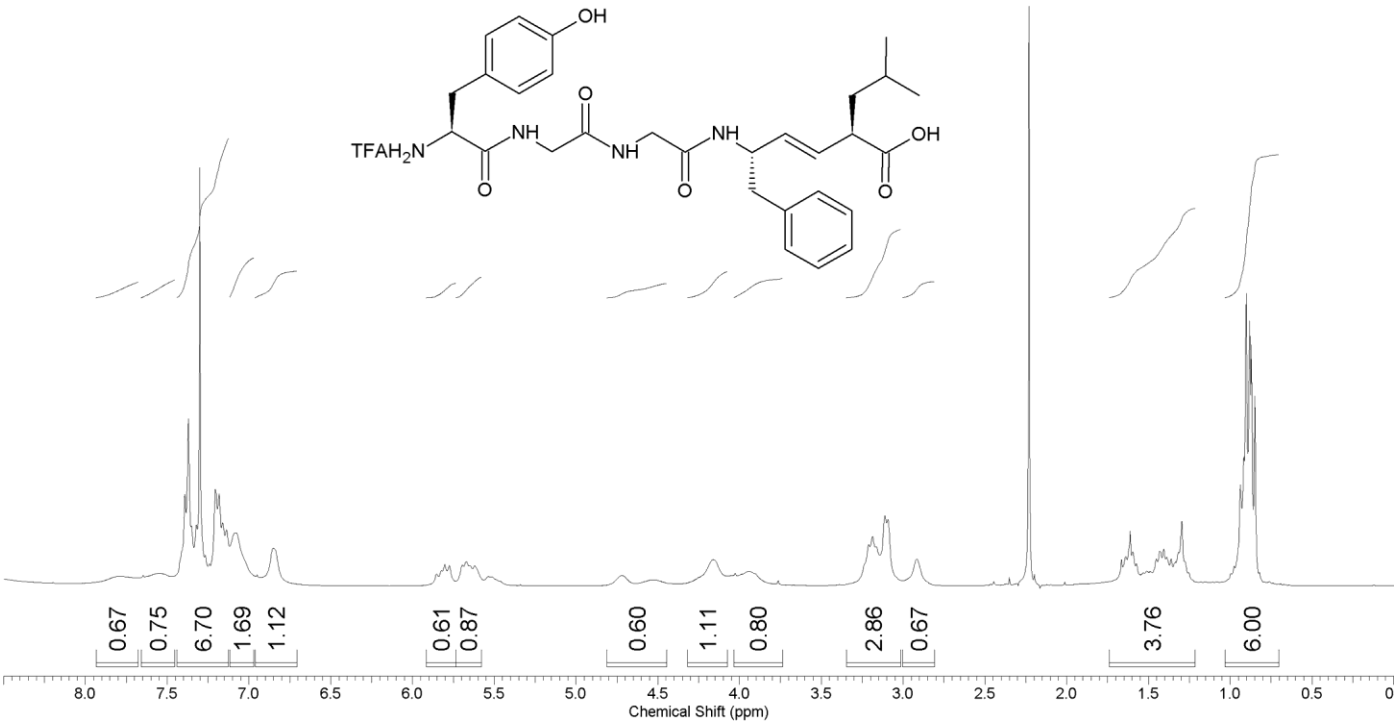


Tyr-Gly-Gly-Phe//Leu (4) and Tyr-Gly-Gly-Phe//DLeu (6)

The amino acid **26** (18.8mg, 0.0720mmol) was dissolved in H_2O (0.5ml) and THF (1ml), then NMM (0.0130ml, 0.120mmol) was added. The solution was stirred at rt for 5min. A solution of the activated ester **28** (664 mg, 1.32mmol) in THF (20ml) was added. The reaction was stirred for 16h at rt. The resulting mixture was concentrated under vacuum and dried under vacuum using toluene 3 times. The protected peptide obtained (500mg, 1.32mmol) was dissolved in DCM (5ml) and TFA (2ml). The reaction was stirred for 2h at rt. The resulting mixture was concentrated under vacuum and dried under vacuum using toluene 3 times. The crude peptide was purified using preparative reverse-phase HPLC, detecting at 280 nm, with a C18 column and using ACN gradient in a 0.1% TFA aq solution (from 1:4 to 2:3). The purity of all fractions was analyzed using an analytical HPLC, detecting at 214 nm, with a C18 column. Using this method the two diastereoisomers were separated.

More polar diastereoisomer : Tyr-Gly-Gly-Phe//Leu (4)

A white solid (6.4mg, 15%). **^{1}H NMR** (300 MHz, $CDCl_3$ + 10% TFA) δ (ppm) 7.81 (br, 1H), 7.47 (br, 1H), 7.38-7.09 (m, 5H), 7.03 (br, 2H), 6.81 (br, 2H), 5.77 (dd, 1H, *J*=8.5 and 15.0 Hz), 5.59 (dd, 1H, *J*=8.0 and 15.0 Hz), 4.69 (br, 1H), 4.13 (br, 1H), 3.88 (br, 1H), 3.17-3.04 (m, 4H), 2.87 (br, 1H), 1.62-1.25 (m, 3H), 0.83 (dd, 6H, *J*=6.5 and 9.5 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$ + 10% TFA) δ (ppm) 180.2, 179.2, 155.2, 135.8, 130.6, 129.4, 129.2, 129.1, 128.7, 128.2, 127.1, 126.9, 116.4, 56.4, 46.6, 40.5, 40.4, 39.4, 25.5, 25.2, 22.4, 22.2, 21.7. **IR** (NaCl) ν (cm^{-1}) 3069, 2963, 2872, 1669, 1517. **MALDI-TOF (m/e, *rel intensity*)** 538.5 (MH^+, 100). **$[\alpha]^{20}_D$** +22.4 (c=0.64, MeOH)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NH
NH
OH
O
O
O
O
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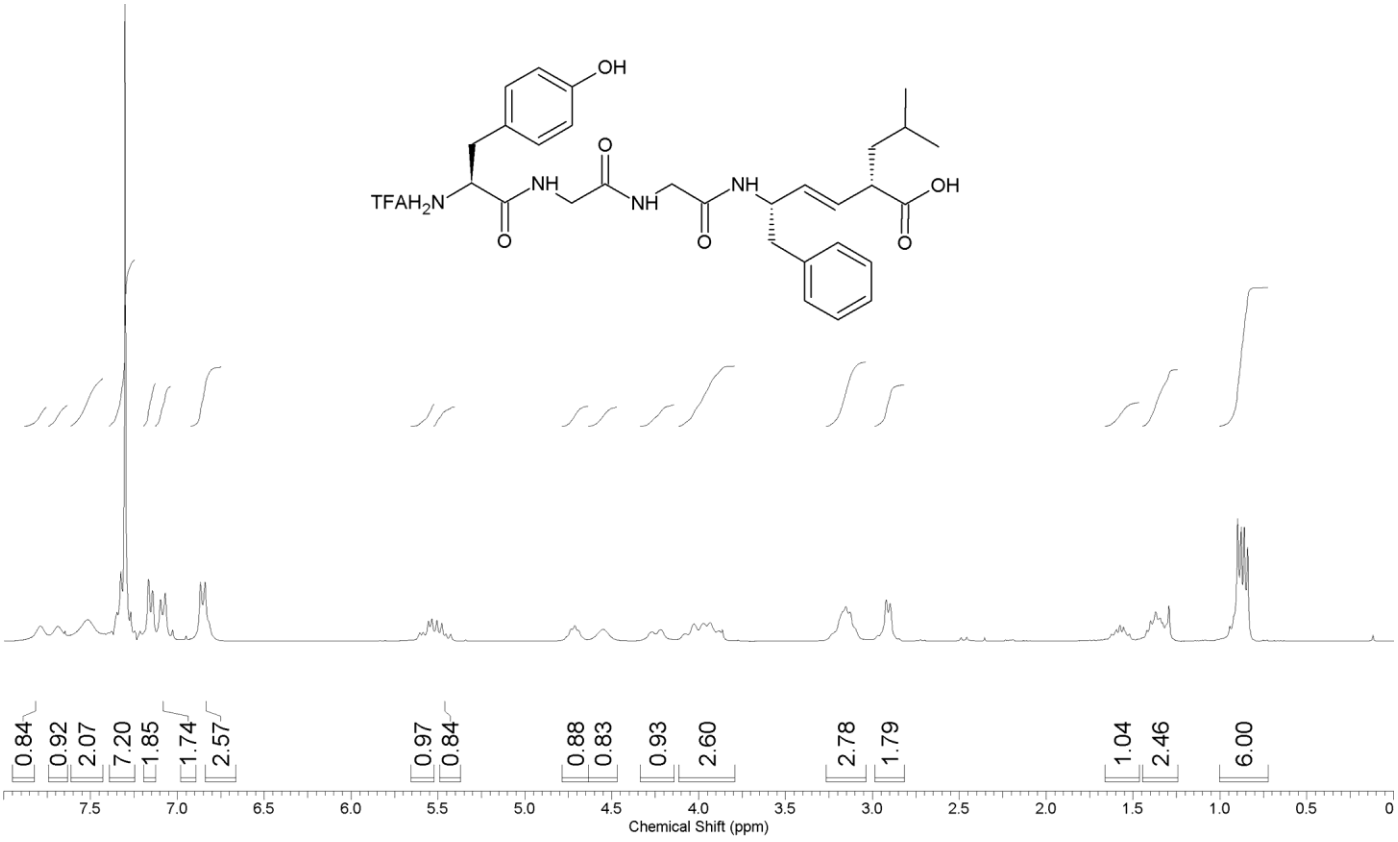
0.75
6.70
1.69
1.12
0.61
0.87
0.60
1.11
0.80
2.86
0.67
3.76
6.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

Less polar diastereoisomer : Tyr-Gly-Gly-Phe//DLeu (6)

A white solid (16.4mg, 39%). **^{1}H NMR** (300 MHz, $CDCl_3$ + 10% TFA) δ (ppm) 7.75 (br, 1H), 7.65 (br, 1H), 7.50 (br, 2H), 7.32-7.20 (m, 3H), 7.11 (d, 2H, *J*=6.5 Hz), 7.04 (d, 2H, *J*=8.0 Hz), 6.81 (d, 2H, *J*=8.0 Hz), 5.53 (dd, 1H, *J*=6.0 and 15.5 Hz), 5.42 (dd, 1H, *J*=8.5 and 15.5 Hz), 4.67 (t, 1H, *J*=7.0 Hz), 4.50 (br, 1H), 4.18-3.82 (m, 4H), 3.11-3.05 (m, 2H), 2.86 (d, 2H, *J*=7.0 Hz), 1.56-1.51 (m, 1H), 1.38-1.25 (m, 2H), 0.82 (dd, 6H, *J*=6.0 and 11.0 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$ + 10% TFA) δ (ppm) 177.1, 175.9, 171.2, 170.8, 131.1, 130.5, 130.0, 129.2, 128.7, 127.1, 124.3, 116.2, 112.4, 55.6, 53.5, 46.6, 43.0, 40.5, 36.4, 31.7, 25.3, 22.5, 21.5. **IR** (NaCl) ν (cm^{-1}) 3287, 3066, 2954, 1667, 1517. **MALDI-TOF (m/e, *rel intensity*)** 539.4 (MH^+, 100). **$[\alpha]^{20}_D$** +31.1 (c=0.85, MeOH)



Wang resin peptide synthesis : [12]

The resins are washed using DMF (3x), *i*PrOH (3x) and DCM (3x), unless stated otherwise.

A) Loading of the resin[13] : The Wang resin (1 g, 0.07mmol/g factory loading) was placed in a sintered glass peptide synthesis vessel. The first amino acid (2 eq), 2,6-dichlorobenzoylchloride (2 eq) and pyridine (4 eq) were added to the resin. The suspension was agitated in a shaker for 16. The resin was washed. All loading were measured by UV quantification of Fmoc release: An aliquot (10mg) of resin was dried under vacuum; a mixture of piperidine (1ml) and DMF (1ml) was added and the suspension was agitated in a shaker for 30 min; a portion of the solution (0.5ml) was diluted in DCM (4.5ml) and its absorbance was read with a UV spectrometer.

Loading of the resin (mmol/g): (Absorbance at 301nm x 10^3 x 20) / (7800 x weight of the aliquot)

The loadings obtained for all resins are mentioned.

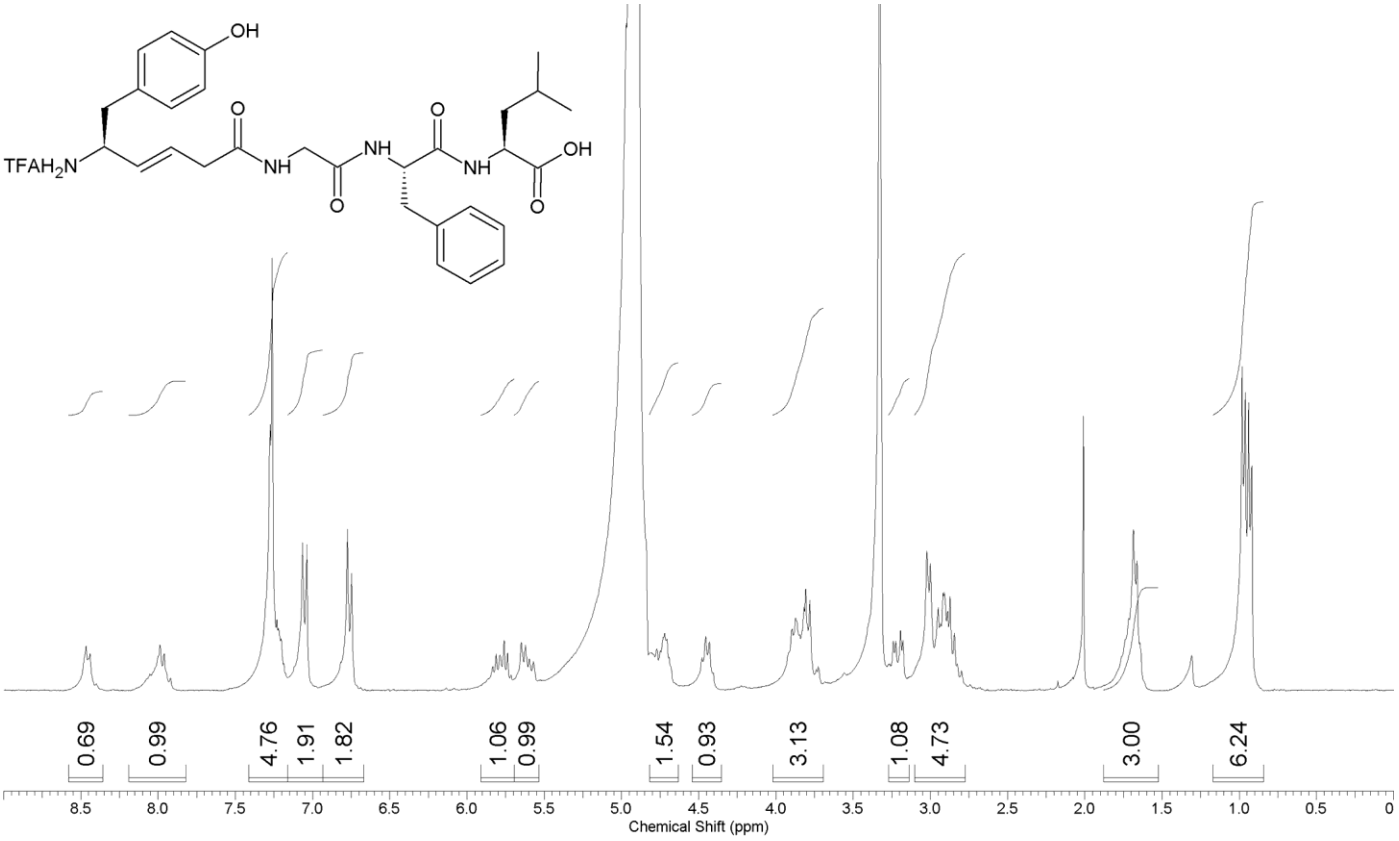
B) After the initial loading[14,15], the remaining free sites were protected using equal amounts of benzoyl chloride and pyridine; the mixture was agitated in a shaker for 4h. For all Fmoc deprotections the resin was treated with 50% piperidine in DMF and the suspension was agitated in a shaker for 20 min. All three couplings were performed using 3 equivalents of protected amino acid and HBTU; with 6 equivalents of NMM in a minimum volume of DMF and the suspension was agitated in a shaker. All couplings procedures were stopped after 16h or after the Kaiser's test result was negative. The amount of modified amino acid used in coupling for each tetrapeptide is mentioned.

C) All the final peptides were cleaved from their resin (3ml of cleavage solution per 1g of resin) in a glass vial and the suspension was stirred for 1h30min with a magnetic stirrer. Cleavage solutions consisted in 95% TFA, 2.5% H_2O, 2.5% TIPS. For peptides **22** and **24**, the following ratio was used: 92.5% TFA, 2.5% H_2O, 2.5% TIPS and 2.5% EDT (1,2-ethanedithiol) was used as the cleavage solution. After cleavage, the mixtures were filtered on cotton and dropped in a large amount of water (20ml). The remaining solvents were concentrated under vacuum and the aqueous solution was frozen and lyophilized. For peptides **21-24**, after cleavage the mixture was filtered on cotton and dropped in Et_2O (50ml) at 0^oC. The obtained precipitates were centrifuged and the major part of the Et_2O was removed by decantation. The remaining precipitates were dissolved in 50% aq AcOH and all the Et_2O was removed from the solution under vacuum. The final aqueous solution was frozen and lyophilized.

D) All crude peptides were purified using preparative reverse-phase HPLC, detecting at 280 nm, with a C18 column and using ACN gradient in a 0.1% TFA aq solution (from 1:9 to 2:3). The purity of all fractions was analyzed using an analytical HPLC, detecting at 214 nm, with a C18 column. All pure fractions were combined, frozen and lyophilized.

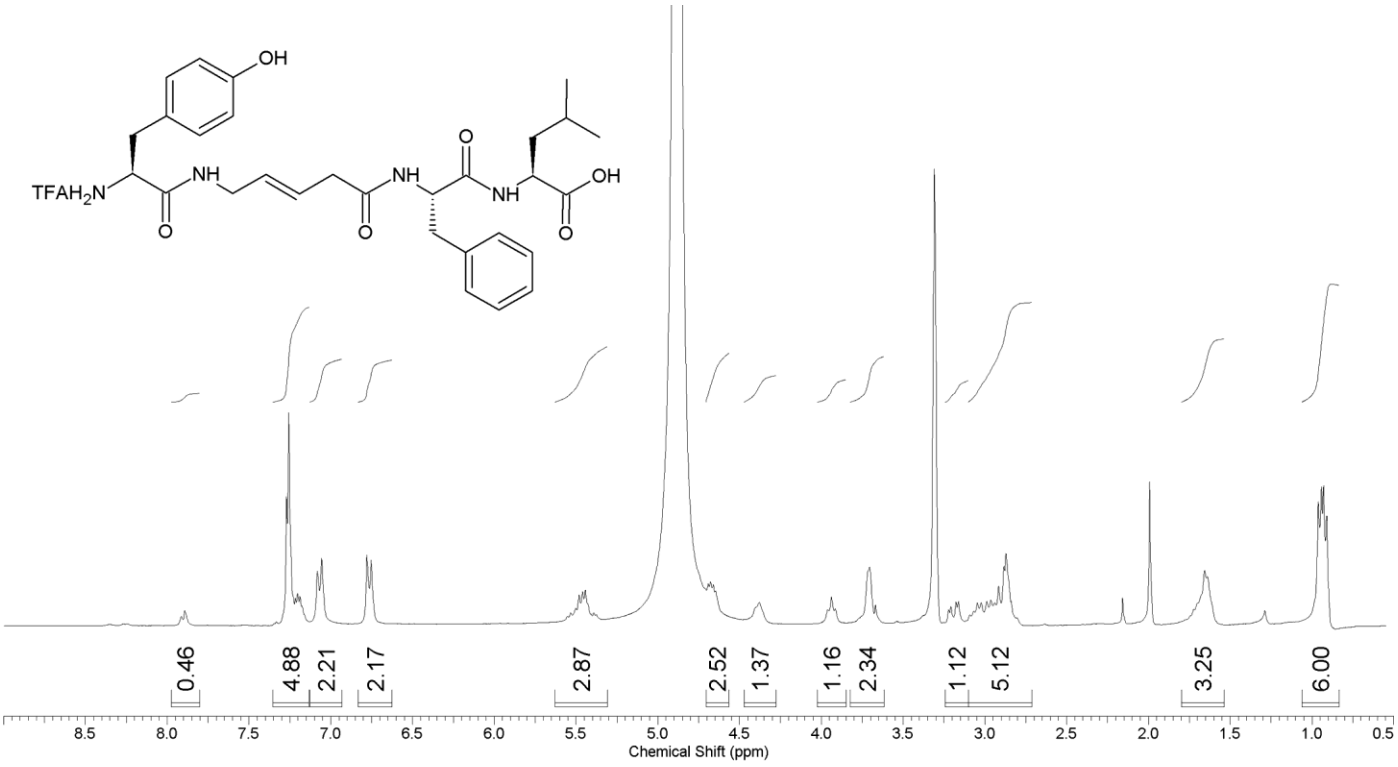
Tyr//Gly-Gly-Phe-Leu (1)

0.5g of resin with a loading of 0.265mmol/g was used. Boc-Tyr(PMB)//Gly **14** (220mg, 0.500mmol) was used in the final coupling. The title peptide was obtained as a white solid (42.8mg, 60%). **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 8.45 (br, 1H), 7.95 (br, 1H), 7.26-7.18 (m, 5H), 7.03 (d, 2H, *J*=8.5 Hz), 6.73 (d, 2H, *J*=8.5 Hz), 5.86-5.51 (m, 2H), 4.81-4.70 (m, 2H), 4.51-4.42 (m, 1H), 3.92-3.73 (m, 3H), 3.27-3.16 (m, 2H), 3.21-2.82 (m, 6H), 1.72-1.63 (m, 3H), 0.95 (d, 3H, *J*=6.0 Hz) 0.91 (d, 3H, *J*=6.0 Hz) . **^{13}C NMR** (75 MHz, CD_3OD) δ (ppm) 172.0, 169.7, 157.0, 136.8, 130.2, 129.7, 129.0, 128.0, 126.4, 125.8, 54.6, 54.1, 41.9, 40.1, 38.4, 38.2, 37.6, 24.5, 21.9, 20.4. **IR** (NaCl) ν (cm^{-1}) 3500-2650 (br), 1652, 1513, 1204. **MALDI-TOF (m/e, *rel intensity*)** 539 (MH^+, 100). **$[\alpha]^{20}_D$** -3.65 (c=0.31, MeOH)



Tyr-Gly//Gly-Phe-Leu (2)

0.5g of resin with a loading of 0.265mmol/g was used. Fmoc-Gly//Gly **16** (120mg, 0.360mmol) was used in the third coupling. The title peptide was obtained as a white solid (16.6mg). **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.86 (br, 1H), 7.27-7.19 (m, 5H), 7.06 (d, 2H, *J*=8.3 Hz), 6.76 (d, 2H, *J*=8.3 Hz), 5.62-5.40 (m, 2H), 4.77-4.64 (m, 2H), 4.38 (br, 1H), 3.90-3.98 (m, 1H), 3.81-3.67 (m, 2H), 3.21-2.84 (m, 6H), 1.77-1.62 (m, 3H), 0.95 (d, 3H, *J*=6.0 Hz) 0.92 (d, 3H, *J*=6.0 Hz). **^{13}C NMR** (75 MHz, CD_3OD) δ (ppm) 173.6, 173.4, 169.5, 158.1, 138.4, 131.6, 130.4, 129.4, 127.7, 126.6, 116.8, 56.1, 55.8, 51.6, 41.9, 39.9, 38.9, 37.9, 26.0, 23.4, 22.0. **IR** (NaCl) ν (cm^{-1}) 3750-3000 (br), 2090, 1631, 1204. **MALDI-TOF (m/e, *rel intensity*)** 539 (MH^+, 100). **$[\alpha]^{20}_D$** +3.93 (c = 0.27, MeOH)

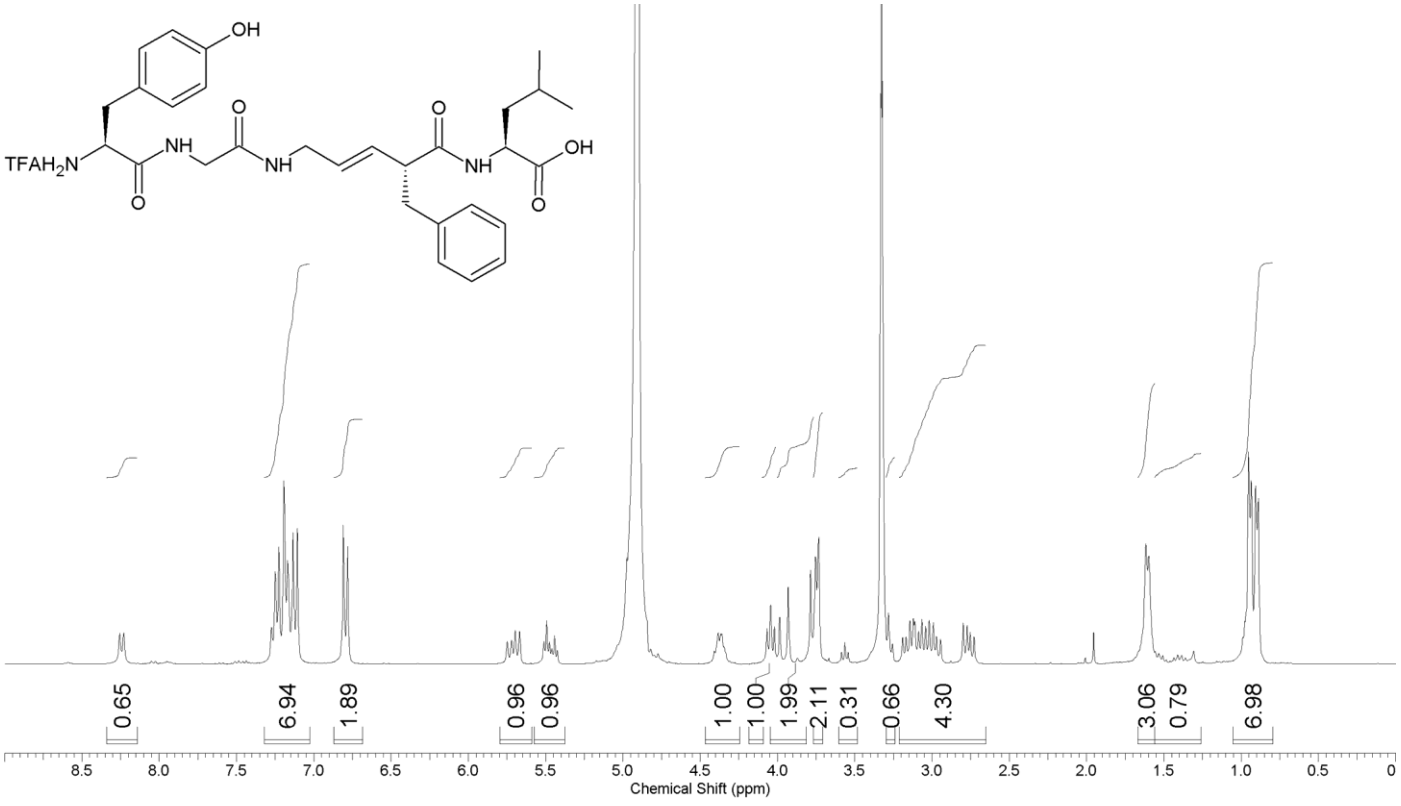


Tyr-Gly-Gly//Phe-Leu (3) and Tyr-Gly-Gly//DPhe-Leu (5)

Since Fmoc-Gly//Phe **20** was racemic two diastereoisomers were obtained with this synthesis. 1g of resin with a loading of 0.160mmol/g was used. Fmoc-Gly//Phe **20** (194mg, 0.450mmol) was used in the first coupling. The two diastereoisomers were separated using preparative reverse phase HPLC.

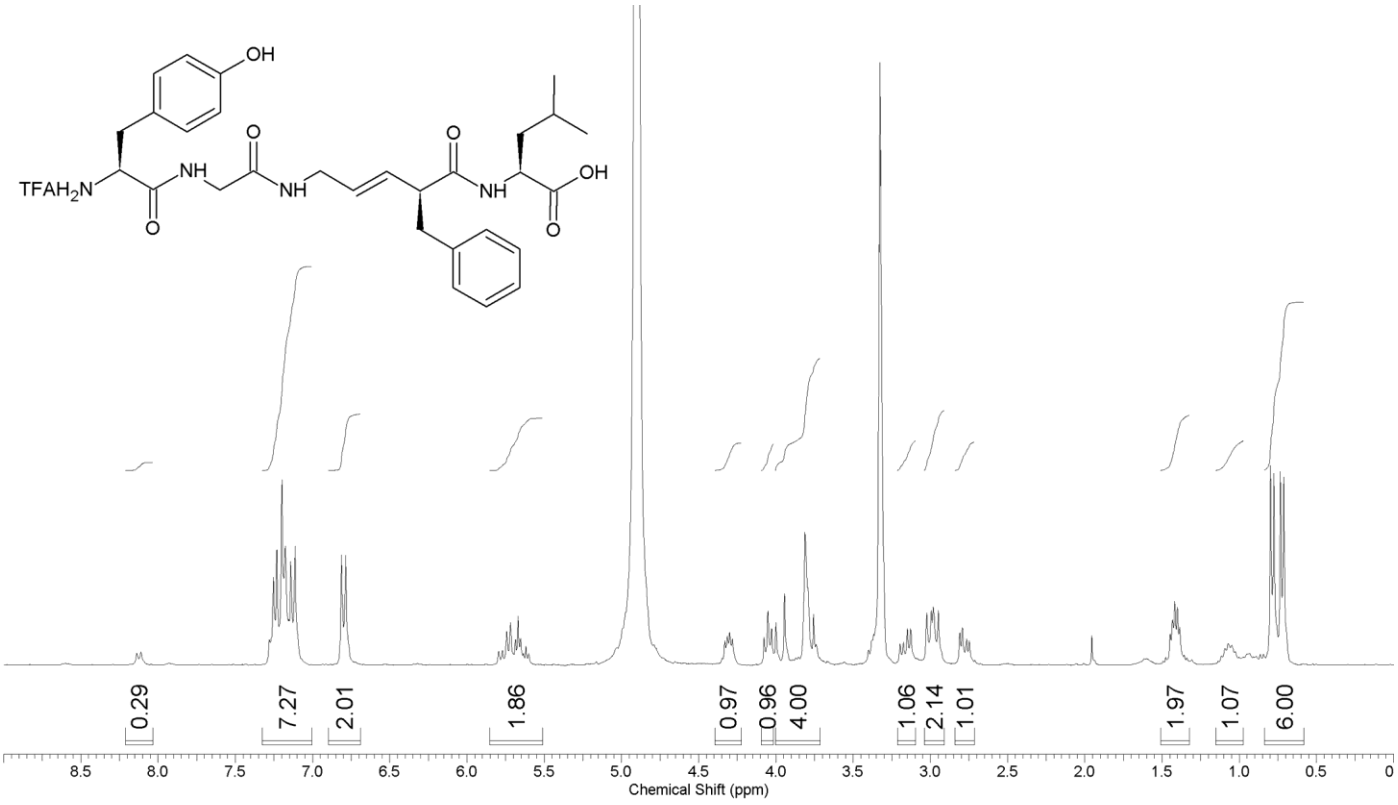
More polar diastereoisomer : Tyr-Gly-Gly//Phe-Leu (3)

The title peptide was obtained as a white solid (77.0mg). **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 8.20 (d, 1H, *J*=8.0 Hz), 7.23-7.06 (m, 7H), 6.75 (d, 2H, *J*=8.5 Hz), 5.64 (dd, 1H, *J*=8.5 and 15.5 Hz), 5.41 (dt, 1H, *J*=6.0 and 15.5 Hz), 4.31-4.38 (m, 1H), 4.00 (t, 1H, *J*=7.0 Hz), 3.94-3.74 (m, 2H), 3.70 (d, 2H, *J*=6.0 Hz), 3.41 (dt, 1H, *J*=6.0 and 15.5 Hz), 3.14-2.68 (m, 4H), 1.56 (d, 2H, *J*=5.5 Hz), 1.54-1.31 (m, 1H), 0.88 (dd, 6H, *J*=6.0 and 13.5 Hz). **^{13}C NMR** (75 MHz, CD_3OD) δ (ppm) 174.6, 174.4, 169.2, 168.9, 156.8, 138.8, 130.1, 130.0, 128.8, 128.0, 127.8, 125.8, 124.6, 115.4, 54.7, 51.3, 50.6, 41.8, 40.2, 40.1, 38.2, 36.2, 24.5, 21.9, 20.4. **IR** (NaCl) ν (cm^{-1}) 3634-2561 (br), 2957, 1670, 1451. **MALDI-TOF (m/e, *rel intensity*)** 539.4 (MH^+, 100). **$[\alpha]^{20}_D$** -1.86 (c=1.47, MeOH)



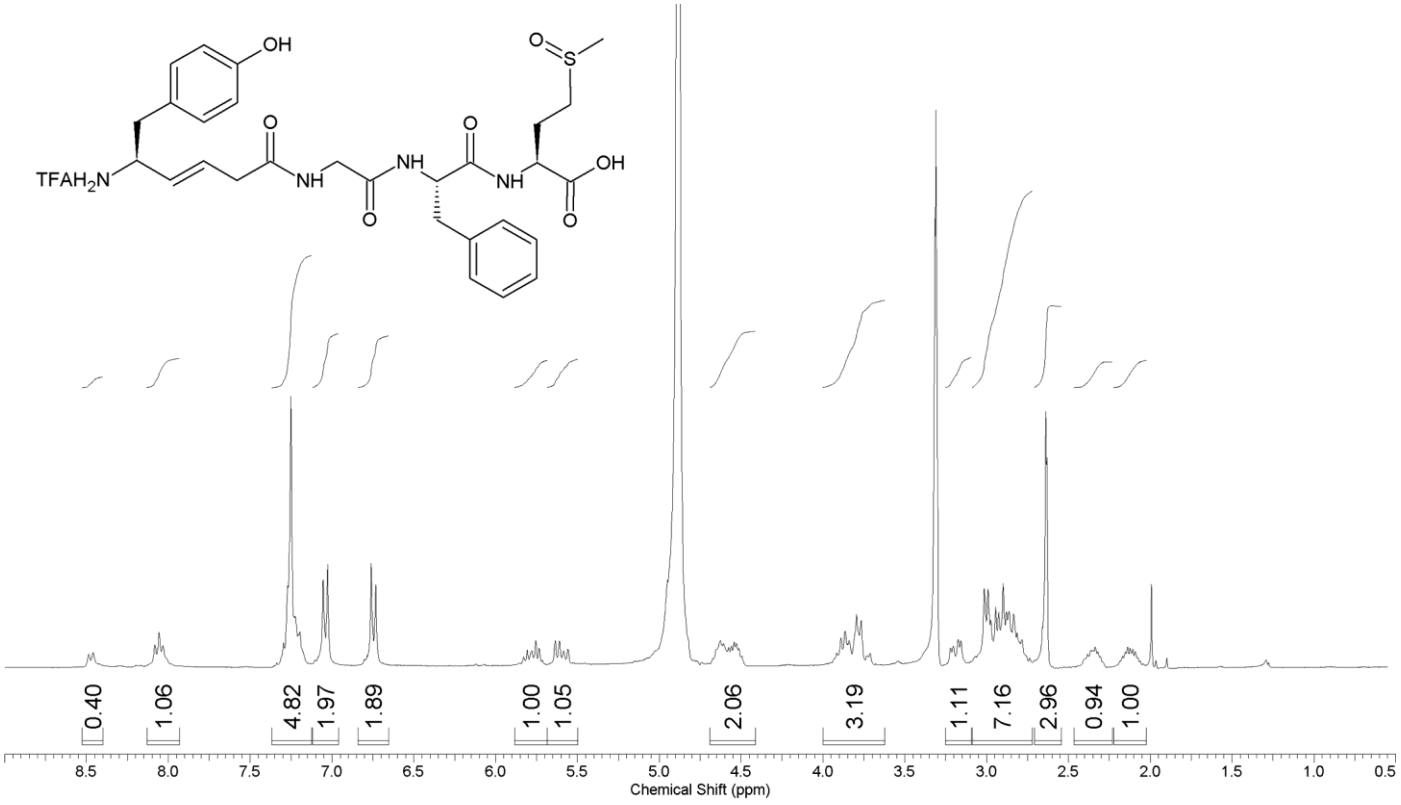
Less polar diastereoisomer : Tyr-Gly-Gly//DPhe-Leu (5)

The title peptide was obtained as a white solid (64.7.0mg). **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 8.05 (d, 1H, *J*=8.0 Hz), 7.23-7.06 (m, 7H), 6.75 (d, 2H, *J*=8.5 Hz), 5.70 (dd, 1H, *J*=7.5 and 15.0 Hz), 5.60 (dt, 1H, *J*=5.0 and 15.0 Hz), 4.28-4.23 (m, 1H), 4.00 (t, 1H, *J*=7.0 Hz), 3.95-3.71 (m, 4H), 3.09 (dd, 1H, *J*=6.5 and 14.5 Hz), 2.98-2.90 (m, 2H), 2.74 (dd, 1H, *J*=6.5 and 14.5 Hz), 1.41-1.34 (m, 2H), 1.10-0.98 (m, 1H), 0.71 (dd, 6H, *J*=6.5 and 19.0 Hz). **^{13}C NMR** (75 MHz, CD_3OD) δ (ppm) 174.6, 174.0, 169.2, 168.9, 156.8, 138.8, 130.3, 130.1, 128.7, 128.0, 127.4, 125.9, 124.6, 115.4, 54.7, 51.5, 50.2, 41.8, 40.3, 40.1, 38.6, 36.2, 23.9, 22.0, 20.2. **IR** (NaCl) ν (cm^{-1}) 3634-2548 (br), 2957, 1670, 1445. **MALDI-TOF (m/e, *rel intensity*)** 539.2 (MH^+, 100). **$[\alpha]^{20}_{D}$** +17.80 (c=1.44, MeOH)



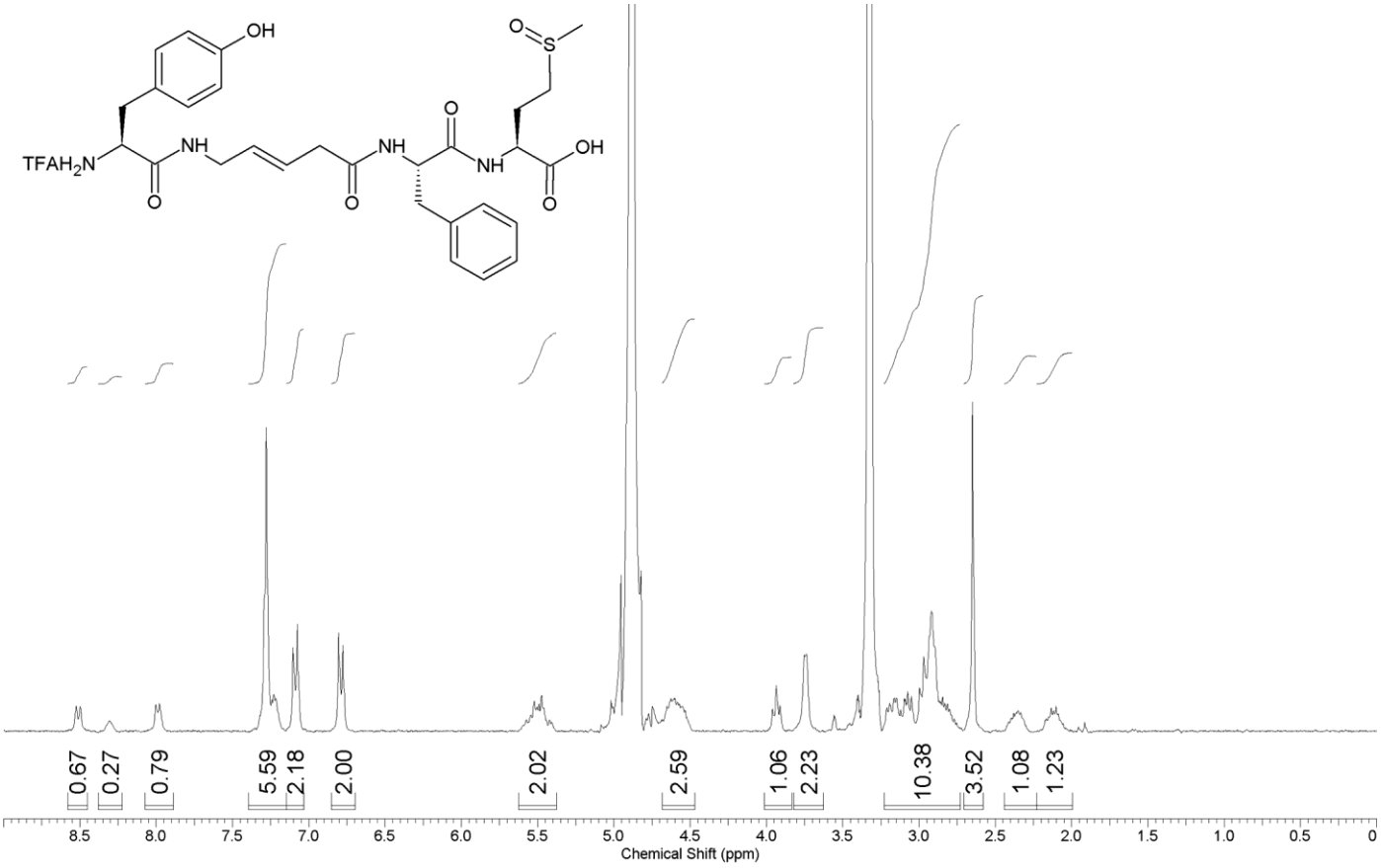
Tyr//Gly-Gly-Phe-Met(O) (7)

0.5g of resin with a loading of 0.250 mmol/g was used. Boc-Tyr(PMB)//Gly **14** (220mg, 0.500mmol) was used in the final coupling. The title peptide was obtained as a white solid (53.6mg). **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 8.45 (br, 1H), 8.10-8.02 (m, 1H), 7.27-7.21 (m, 5H), 7.04 (d, 2H, *J*=8.5 Hz), 6.74 (d, 2H, *J*=8.5 Hz), 5.85-5.56 (m, 2H), 4.69-4.51 (m, 2H), 3.91-3.73 (m, 3H), 3.21-2.81 (m, 10H), 2.66 (s, 3H), 2.41-2.27 (m, 1H), 2.21-2.08 (m, 1H). **^{13}C NMR** (75 MHz, CD_3OD) δ (ppm) 172.4, 172.2, 172.0, 169.9, 156.4, 136.8, 130.2, 129.8, 128.9, 128.1, 126.4, 125.8, 115.2, 54.6, 51.4, 49.6, 42.0, 38.4, 38.2, 37.1, 36.8, 36.7, 24.5. **IR** (NaCl) ν (cm^{-1}) 3750-3100 (br), 2103, 1646, 1518. **MS (m/e, *rel intensity*)** 573 (MH^+, 100). **$[\alpha]^{20}_D$** +2.03 (c=1.97, MeOH)



Tyr-Gly//Gly-Phe-Met(O) (8)

0.5g of resin with a loading of 0.250 mmol/g was used. Fmoc-Gly//Phe **20** (120mg, 0.360mmol) was used in the second coupling. The title peptide was obtained as a white solid (56.1mg). **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 8.51 (br, 1H), 8.29 (br, 1H), 7.98 (br, 1H), 7.27-7.19 (m, 5H), 7.06 (d, 2H, *J*=8.5 Hz), 6.76 (d, 2H, *J*=8.5 Hz), 5.61-5.32 (m, 2H), 4.69-4.35 (m, 2H), 3.98-3.89 (m, 1H), 3.72 (d, 2H, *J*=4.4 Hz), 3.08-3.03 (m, 2H), 2.98-2.82 (m, 6H), 2.63 (s, 3H), 2.40-2.26 (m, 1H), 2.21-2.06 (m, 1H). **^{13}C NMR** (75 MHz, CD_3OD) δ (ppm) 173.9, 173.7, 173.6, 169.4, 158.2, 138.2, 131.6, 130.4, 129.4, 127.8, 126.6, 126.1, 116.8, 56.1, 41.9, 39.8, 38.2, 37.9, 26.0. **IR** (NaCl) ν (cm^{-1}) 3800-2520 (br), 1664, 1512, 1201. **MS (m/e, *rel intensity*)** 573 (MH^+, 100). **$[\alpha]^{20}_D$** +8.10 (c=0.51, MeOH)



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